U.S. FOOD & DRUG ADMINISTRATION

Pediatric Drug Development and Bayesian Method

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Disclaimer

This talk reflects the views of the speaker and should not be considered to represent FDA's views or policies

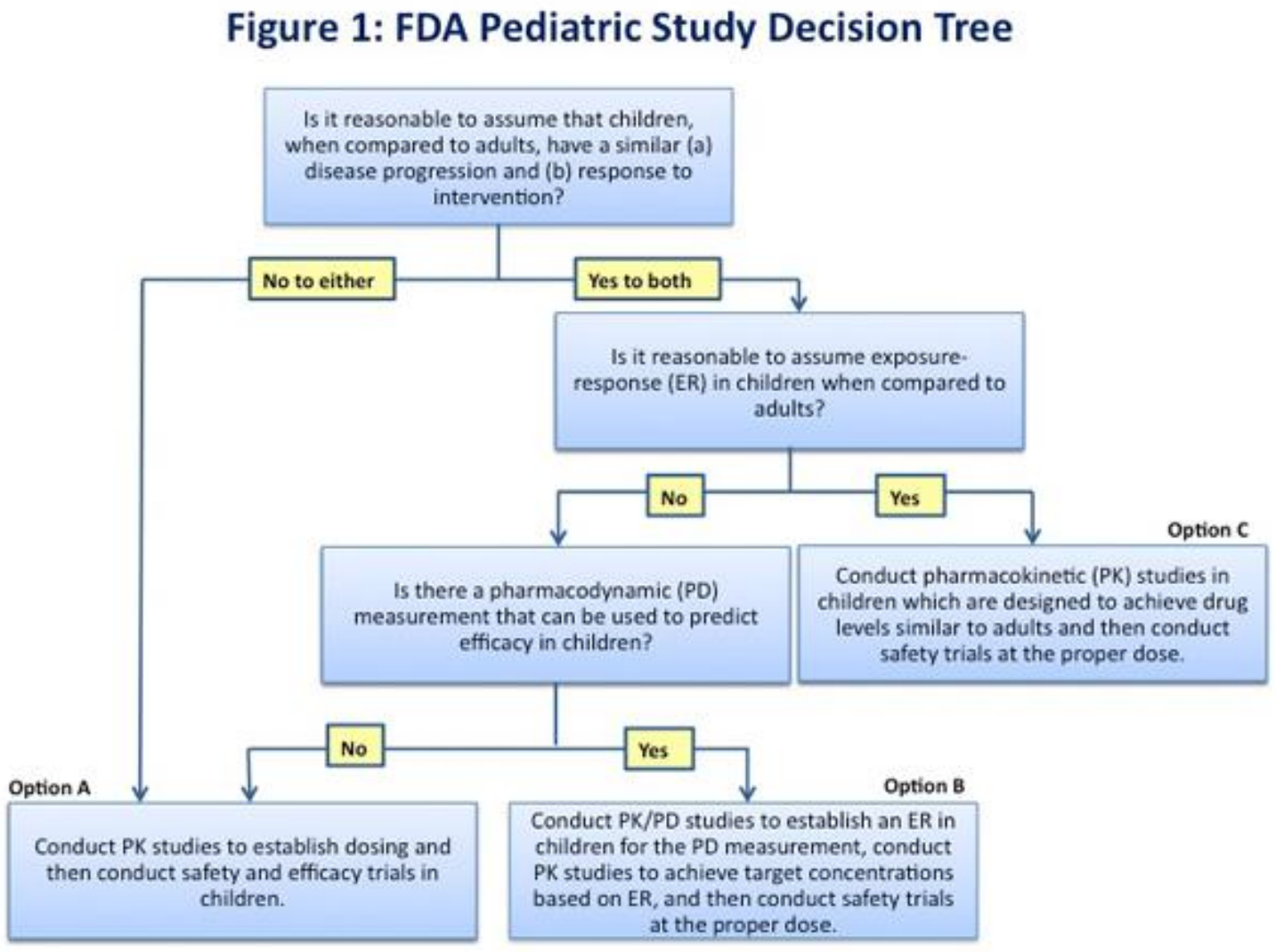
Outline

- Principles of pediatric drug development
- Challenges
- Applicability of Bayesian
- Case examples
- Conclusions

Principles of Pediatric Drug Development

- Children are not miniature adults
  - Different physiologic, developmental, psychologic, and pharmacologic characteristics; Differ across pediatric spectrum
  - Different in how they metabolize and respond to drug: suboptimal therapy, unexpected response, AE, and toxicity
- Legal requirement of **SUBSTANTIAL EVIDENCE** to establish the effectiveness of drug
- For disease/condition that exists exclusively in children
  - Adequate and well-controlled trial(s)
- For disease/condition that exists in both adults and children
  - Adequate and well-controlled trial(s)
  - Extrapolation may be allowed under some circumstances

Extrapolation vs. No Extrapolation



https://www.fda.gov/science-research/pediatrics/pediatric-science-and-research-activities
https://pediatrics.aappublications.org/content/128/5/e1242

Challenges

- **Low enrollment**
  - Limited disease population, fear of the risk, concern over randomization to placebo, drug off-label use
- **High dropout**
  - Too many study visits, number of invasive procedures, feel drug is ineffective, concern about risk/benefit profile
- **Ethical considerations**
  - Participants are expected to benefit from clinical trials, benefit and risk balance, minimizing risk by minimizing the number of participants at design stage
- **Delayed study initiation**
  - Formulation can take time, waiting for adult approval, safety considerations

Operational challenges + Design challenges + Analysis challenges

Innovative Thinking and Strategies

Span over the entire drug development cycle – Opportunity for statisticians to play an essential role

- Global pediatric trial – MRCT (ICH E17)
- Age-staggered enrollment and initiation
- Enrolling adolescents into adult trials
- Master protocols – umbrella, platform, basket
- Real World Data – Historical (external) Controls
- Bayesian methods

Applicability of Bayesian Methods in Pediatric Trials

Similarities between adult and pediatric patients on the course of disease and effect of drug; Similar study design, conduct, and endpoints; Adult/older age group data are available and hard to ignore

- Leveraging adult/older age group data

Ethical considerations: Limit the number of exposure; Stop the trial early for efficacy or futility

- Borrowing external data as control / augment the concurrent control when reasonable
- Update knowledge or decision-making when information accumulates, e.g. Bayesian sequential monitoring

Case Example 1

- Chronic Hepatitis C – MAVYRET
  - Approved for adults in 2017
  - Course of disease and the effect of the drugs are sufficiently similar in adults and pediatric patients, but not identical
  - Extrapolation of efficacy from PK data to support approval, SVR12 provides supportive evidence of efficacy
- Pediatric clinical trial
  - Open-label, single-arm, adolescent subjects 12 to <18 years (n=47).
  - PK data were comparable to adults. SVR12 rate was 100% (47/47)
  - Approved in May, 2019. First treatment for all genotypes of HCV in pediatric patients

https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-all-genotypes-hepatitis-c-pediatric-patients
https://www.rxabbvie.com/pdf/mavyret_pi.pdf

A Related Hypothetical Scenario

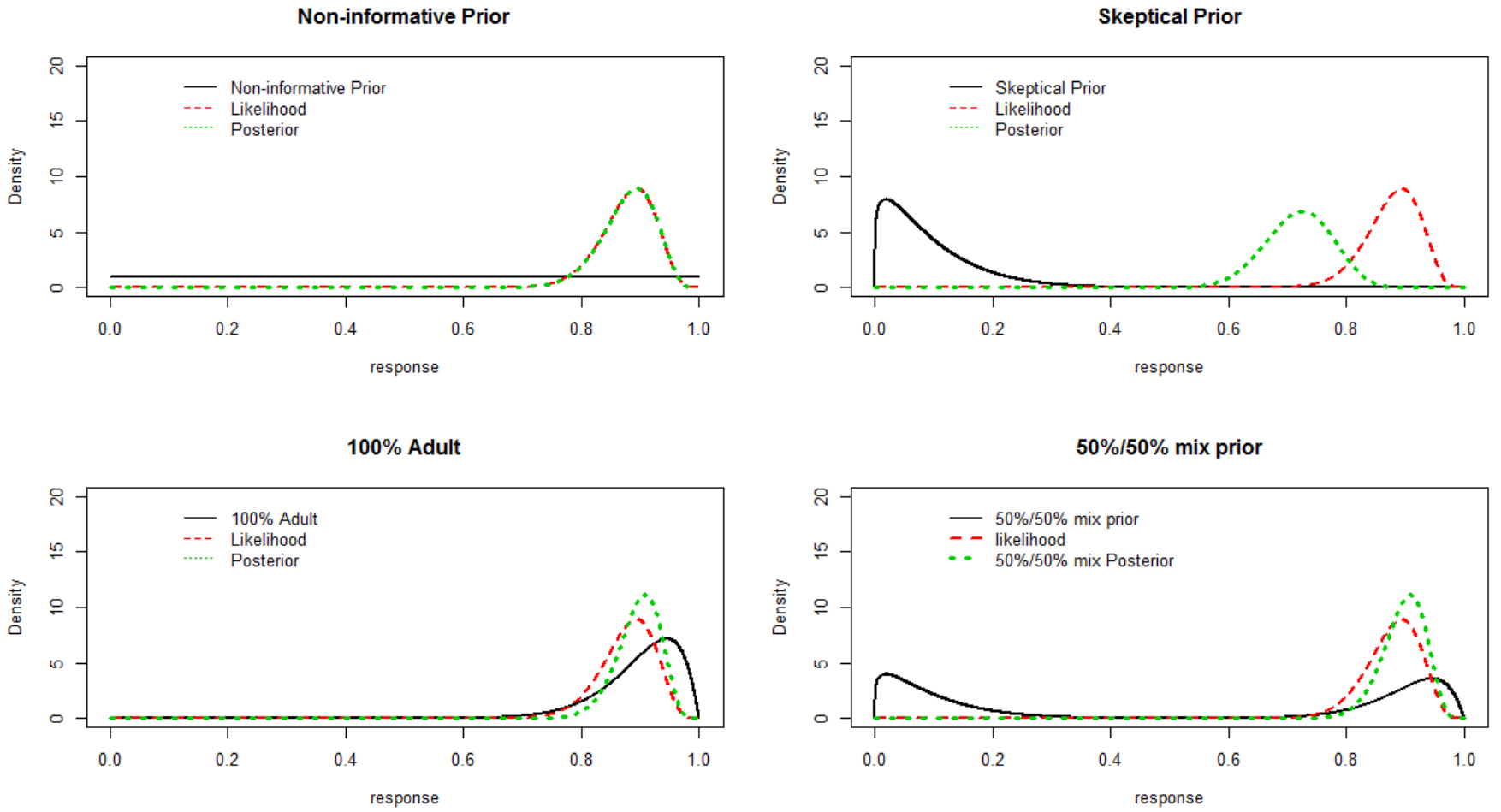
- What if SVR12 is 95%, 90%, 85%…?
- Adult SVR12 – genotype 1-6, no cirrhosis, treatment-naïve, treatment experienced (peginterferon, ribavirin, sofosbuvir)

Adult	**N=663**	**GT1-6: 93% - 100%** **95% CI for GT1-6 ranges 82%, 100%**

- Bayesian analysis – interested in posterior prob. of SVR12 > xx% (e.g. 82%, 30%)
  - Selection of prior
  - Prior=$(1-\alpha) \times f(D) + \alpha \times g(D)$
  - f(D): skeptical prior/non-informative prior
  - g(D): adult posterior
  - α =P(applicability of adult results)

A Related Hypothetical Scenario

Posterior Distribution



A Related Hypothetical Scenario

Posterior Probability of Efficacy

Prior	If observed pediatric SVR 12 = 89%		
	Bayesian Estimate (95% Cred. Int.)	Post. Prob. SVR12 > 82%	Post. Prob. SVR12 > 30%
Non-informative	88.3 (77.3, 95.3)	88.5%	>99.9%
Skeptical	72.0 (59.9, 82.3)	2.9%	>99.9%
100% adult	89.9 (81.3, 95.6)	96.5%	>99.9%
50%/50% mixture	89.9 (81.2, 95.6)	96.5%	>99.9%

Case Example 2

Benlysta (belimumab)

Approved for adult patients with active, seropositive lupus erythematosus (SLE) in 2011.

- A pediatric post-marketing study was required under PREA:
  - A randomized, double-blind, placebo-controlled trial targeting to enroll 100 pediatric subjects 5 to 17 years of age with active systemic SLE
- Study was not fully powered by design. Efficacy was planned to be descriptive; no formal statistical hypothesis testing
- Trial was started in 2012. Due to difficulties in enrolling patients, the overall target enrollment was reduced to 70 in 2016. The study was completed in 2018
- There was no approved treatment for pediatric SLE patients

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125370s064,761043s007lbl.pdf
https://www.fda.gov/media/127912/download

Case Example 2 - continued

Primary Efficacy Result

Primary endpoint: response rate at Week 52 as assessed by SRI (SLE Responder Index - composite efficacy measure, used in the approved adult trials)

	Pediatric Study		Adult Study 1		Adult Study 2	
	Placebo N=40	**Belimumab N=53**	**Placebo N=275**	**Belimumab N=273**	**Placebo N=287**	**Belimumab N=290**
Response, n(%)	17 (43.6)	28 (52.8)	93 (34)	118 (43)	125 (44)	167 (58)
Observed difference	9.2%		9%		14%	
Odds ratio (95% CI)	1.5 (0.6, 3.5)		1.5 (1.1, 2.1)		1.8 (1.3, 2.6)	

Secondary endpoint: proportion of subjects meeting PRINTO/ACR Juvenile SLE Response Evaluation criteria for improvement at Week 54, and the 5 components of this endpoint – all results favor the belimumab group

Post-hoc exploratory analyses of biomarkers: all results favor the belimumab group

Source: BENLYSTA® Multi-disciplinary Review and Evaluation https://www.fda.gov/media/127912/download

Case Example 2 - continued

A Post-hoc Bayesian Analysis Was Requested by FDA

Comparisons between adults and pediatric patients/studies

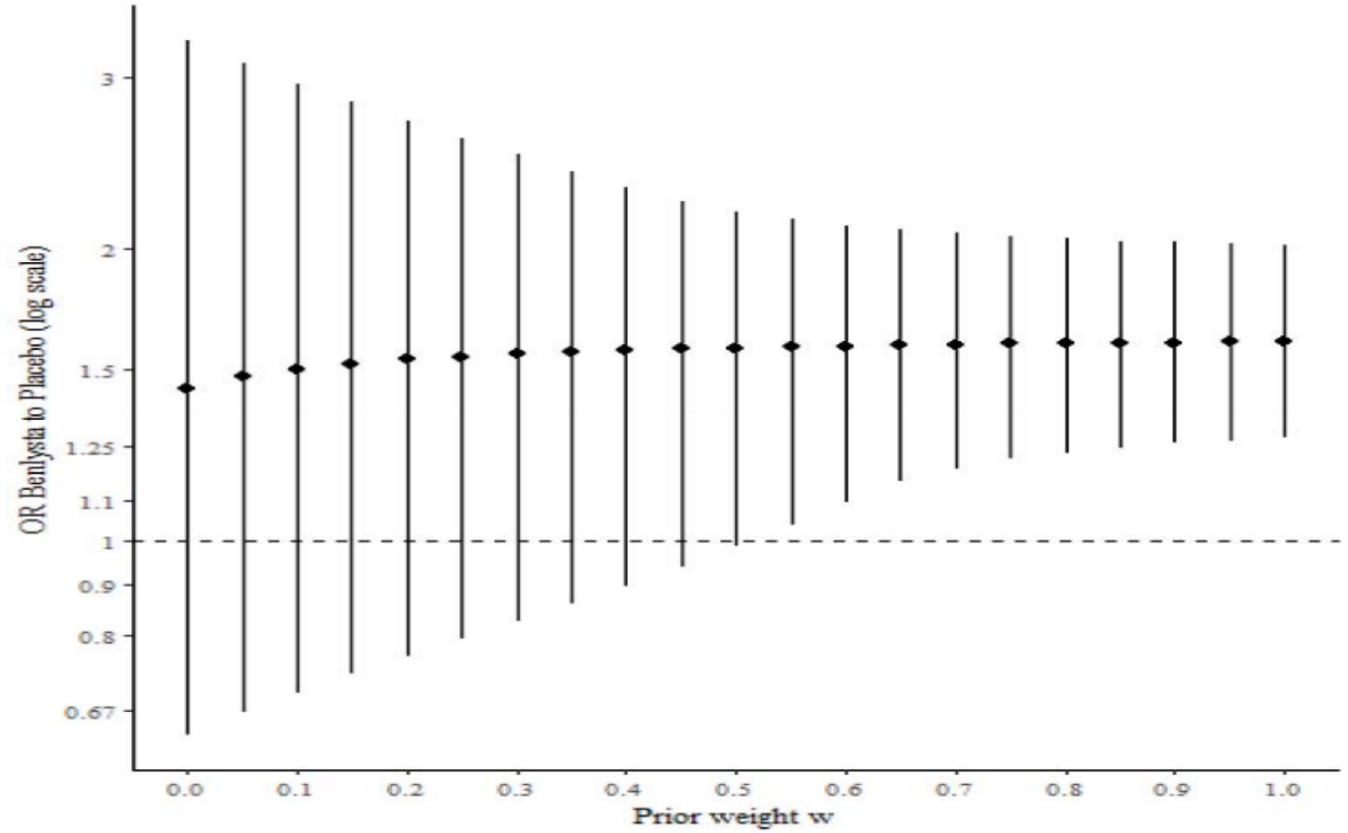
- Disease and patient response to the treatment are likely to be similar
- Same efficacy endpoints
- Study design and conduct were highly similar

Borrow information from adult studies

- Bayesian mixture prior - Determine the range of weight where the posterior probability of efficacy exceeds the thresholds of 97.5%

- Prior=(1- α) × f(D) + α × g(D)
  - f(D): skeptical prior - $N(0, m \times s_P^2)$
  - g(D): adult posterior - $N(y_A, s_A^2)$
  - y_A: log odds ratio from adult studies
  - s_A^2: variance of adult log odds ratio
  - s_P^2: variance of pediatric log odds ratio
  - m: was chosen so that the effective sample size of this component worth one pediatric subject per arm
  - α : weight

Case Example 2 - continued



- A prior weight of 0.55 or larger led to the posterior probabilities > 97.5%
- ≥ 0.55 weight on the relevance of the adult information is reasonable
- Approved in pediatric population (≥ 5 years) in 2019

Source: BENLYSTA® Multi-disciplinary Review and Evaluation https://www.fda.gov/media/127912/download

Case Example 3

PREVAIL II and PALM – A Story of ZMapp

- PREVAIL II – A randomized, controlled trial with a "barely Bayesian" design
  - Prior: Independent uniform distribution on [0, 1] for arms A and B
  - Posterior probability: Observe data -> update priors to posterior distributions -> compute posterior probability of $p_A < p_B$
  - Primary analysis: Posterior probability of Day 28 mortality; Pre-specified threshold for success was 97.5%
  - Aimed to enroll 200 patients (1:1), but ended up with 72 patients because of the waning Ebola epidemic.
  - Result: Mortality rates were 22% vs 37% for ZMapp+SOC vs SOC; Posterior probability that ZMapp was better was 91.2%

https://www.nejm.org/doi/full/10.1056/NEJMoa1604330 https://journals.sagepub.com/doi/full/10.1177/1740774515620145
https://academic.oup.com/jid/article/213/12/1906/2572167

Case Example 3 - continued

PREVAIL II and PALM – A Story of ZMapp

- PALM – A randomized, controlled platform trial
  - Four treatment arms: ZMapp, remdesivir, Mab114, REGN-EB3 (1:1:1:1)
  - Targeted sample size was 725 in total
  - Primary endpoint: Day 28 mortality
  - Comparisons were restricted to patients enrolled concurrently
  - Results: ZMapp arm was discontinued early due to high mortality

Population	ZMapp	Remdesivir	Difference, Remdesivir vs. ZMapp	MAb114	Difference, MAb114 vs. ZMapp	REGN-EB3	ZMapp Subgroup	Difference, REGN-EB3 vs. ZMapp Subgroup
	no. of deaths/ total no. (%)	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*	*no. of deaths/ total no. (%)*	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*
Overall	84/169 (49.7)	93/175 (53.1)	3.4 (–7.2 to 14.0)	61/174 (35.1)	–14.6 (–25.2 to –1.7)*	52/155 (33.5)	79/154 (51.3)	–17.8 (–28.9 to –2.9)*
Patients with high viral load†	60/71 (84.5)	64/75 (85.3)	0.8 (–15.3 to 17.2)	51/73 (69.9)	–14.6 (–33.0 to –0.5)	42/66 (63.6)	56/65 (86.2)	–22.5 (–41.8 to –5.1)
Patients with low viral load†	24/98 (24.5)	29/100 (29.0)	4.5 (–9.1 to 19.1)	10/101 (9.9)	–14.6 (–32.4 to –2.6)	10/89 (11.2)	23/89 (25.8)	–14.6 (–32.6 to –2.3)

https://www.nejm.org/doi/full/10.1056/NEJMoa1910993

Conclusion

- Challenges exist in pediatric drug development
- Demonstration of substantial evidence is required
- Bayesian methods can be useful in pediatric trials
- Prior beliefs affect the estimates of efficacy
- Type I error rate may be inflated depending on the choice of prior
- Pre-specification is key
- A promising result may not be a real effect for both pediatric and adult studies
- Early interaction with the FDA is encouraged

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Thank You!