Challenges and Opportunities – Regulatory and Statistical Considerations in Pediatric Drug Development

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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

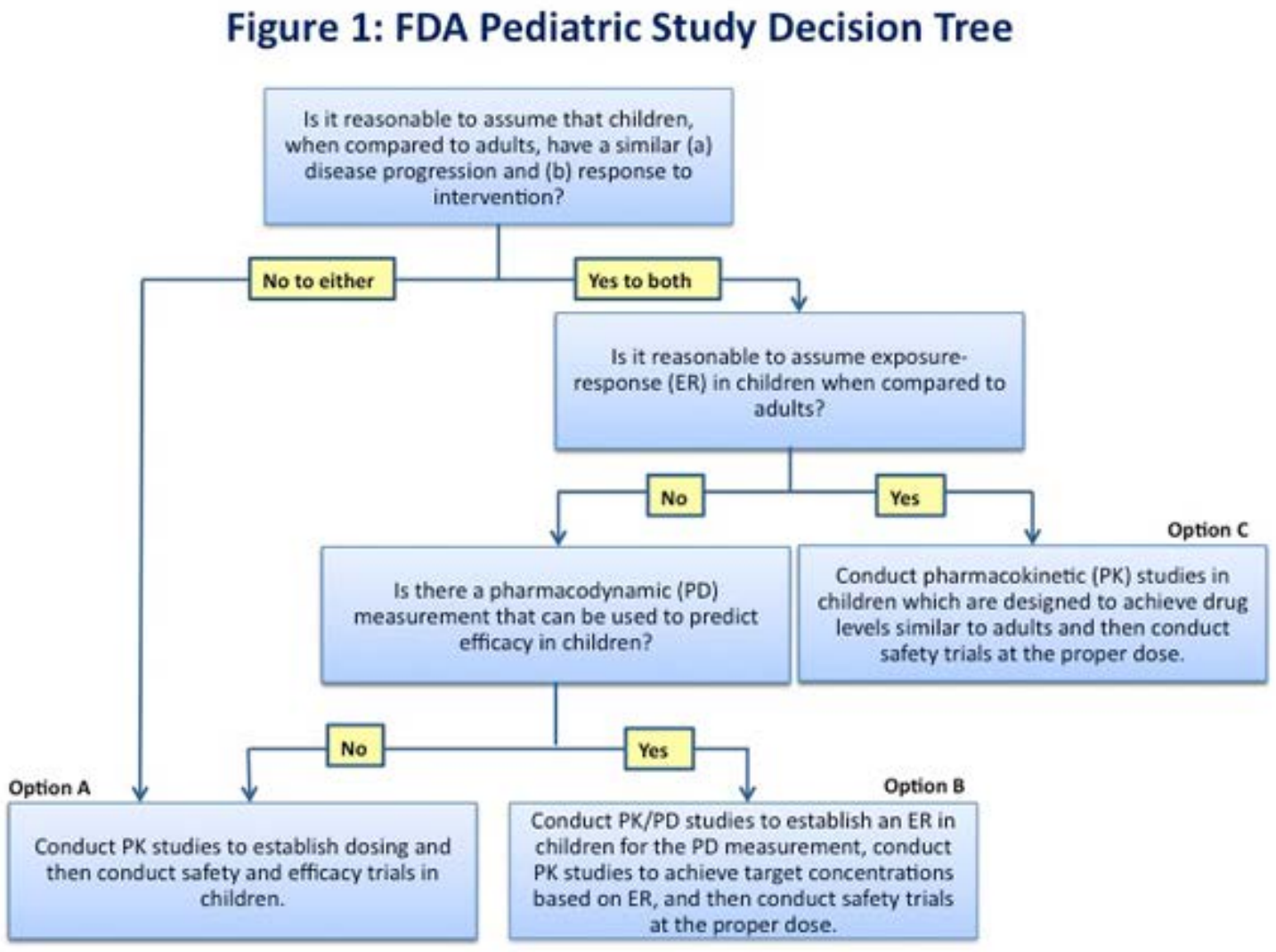
Outline

- Principles of pediatric drug development
- Challenges
- Strategies
- 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)
  - Planning: consult with regulatory authorities early
  - Regional variability/difference: intrinsic and extrinsic factors
  - Stratification: by region
  - Sample size: overall, allocation to regions
- Age-staggered enrollment and initiation
  - Start from older children -> younger ones
  - Enrollment of younger age group can begin given the likelihood of benefit in older age group
  - Leveraging older group data to younger group

Strategies - continued

- Enrolling adolescents into adult trials

  Oncology trials:
  - In early phase and confirmatory trials
  - Same histology and biologic behavior of the cancer/molecular target of the drug in both adult and adolescent
  - Safety monitoring should evaluate age-related differences and developmental toxicities

  Non-Oncology trials:
  - In confirmatory trials
  - Sufficient similarity in disease progression and anticipated response to therapy between adult and adolescent
  - Prospect of direct benefit to pediatric patients
  - Adequate preliminary dosing information and clinical safety data
  - Safety monitoring
  - Stratification, sample size for sub-population
  - Example: HIV, HCV, asthma, etc.

Strategies - continued

- Master protocols – umbrella, platform, basket (Woodcock and LaVange, 2017)

Type	Objective
Umbrella	Multiple therapies for a single disease
Basket	A single therapy for multiple diseases
Platform	Multiple therapies for a single disease. Therapies are allowed to enter or leave the platform

  - Involve multiple stakeholders, utilize trial network with infrastructure, and have a common protocol
  - Need increased planning and coordination
  - Innovative design and analysis: adaptive, Bayesian, response-adaptive randomization, shared control, sequential analyses with stopping early for success or failure, etc.

Strategies - continued

- Real World Data – Historical (external) Controls
  - Concerns: May have systematic differences between non-concurrent treatment groups
  - Well-documented, highly predictable disease course that can be objectively measured
  - Expected drug effect is large, self-evident, and temporally closely associated with the intervention

<u>Natural History Studies</u>

  - In-depth understanding of disease: prospectively designed, protocol driven
  - Comparability: systematically captured data using methodologies relevant to the interventional trials

Strategies - continued

- Bayesian methods
  - Leveraging adult /older age group data if relevant
  - Borrowing external data as control / augment the concurrent control when reasonable
  - Update knowledge or decision-making when information accumulates, e.g. sequential monitoring to offer options to stop trial early for both efficacy and futility
  - Some commonly used methods
    - Mixture prior
    - Power prior
    - Commensurate prior
    - Bayesian hierarchical model

Statistical Working Group

ASA Biopharm Section Pediatric Working Group

- Proposed by Office of Biostatistics, CDER, FDA
- Collaboration with industry, academia, EMA, PMDA, and Health Canada
- Subgroups: RWD, statistical extrapolation, stat issues in genomic data, stat evidence for using biomarker as trial endpoint, composition of trial population, etc.

Case Example 1

- Chronic Hepatitis C – MAVYRET
  - Approved for adult 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

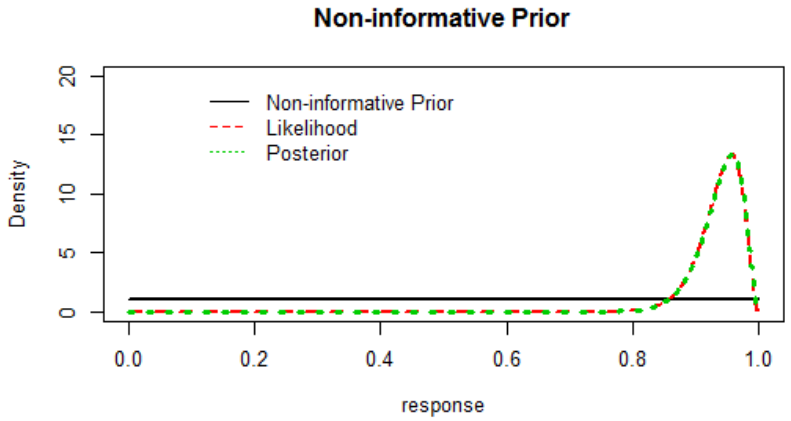
- What if SVR12 is 95%, 90%, 85%…?
- Adult SVR12 – genotype 1-6, no cirrhosis, treatment-naïve, treatment experienced (peginterferon, ribavirin, sofosbuvir)

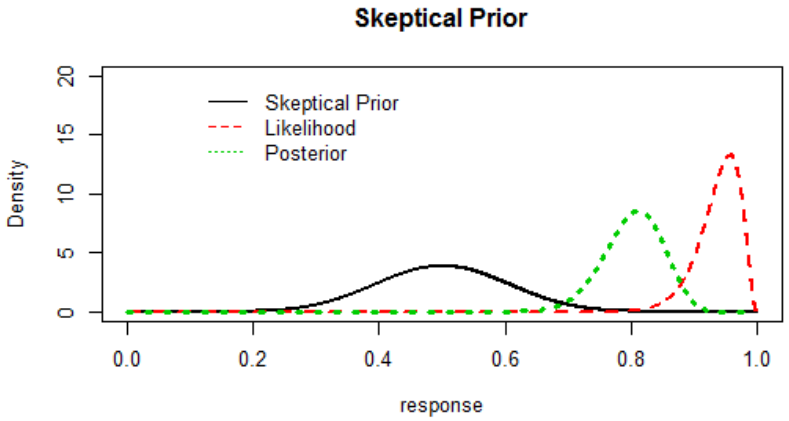
Adult	**N=663**	**GT1-6: 93% - 100%** **95% CI for GT1-6 ranges 82%, 100%**

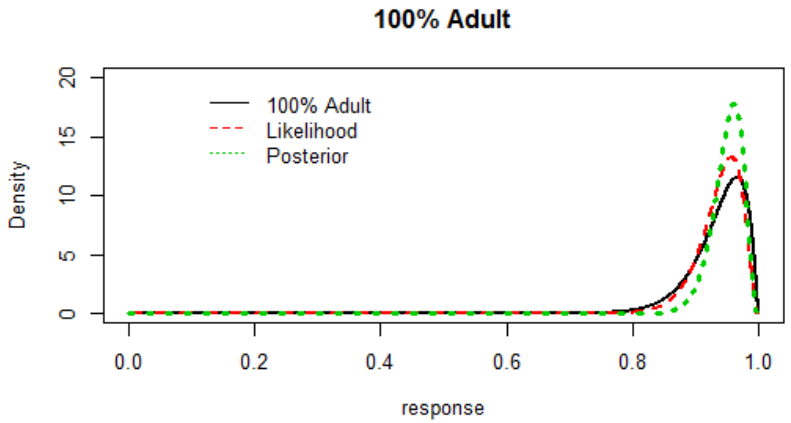
- Bayesian analysis – interested in posterior prob. of SVR12 > xx%
  - Selection of prior
  - Prior=(1-a)*f(D) + a*g(D)
  - f(D): skeptical prior/non-informative prior
  - g(D): adult posterior
  - a=P(applicability of adult results)

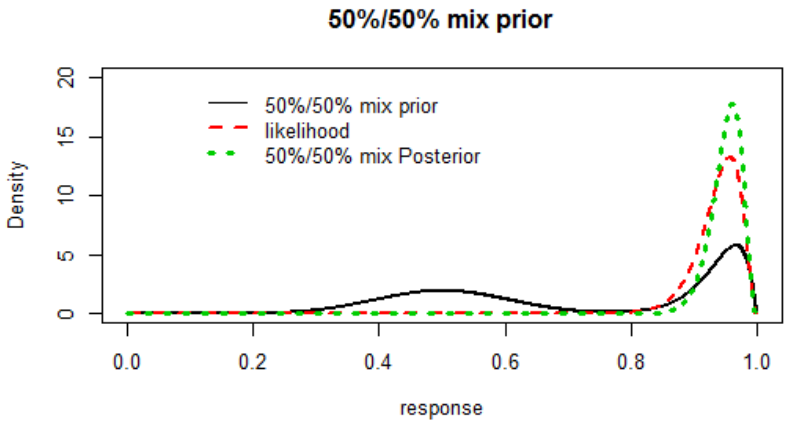
A Related Hypothetical Scenario

Posterior Distribution









A Related Hypothetical Scenario

Posterior Probability of Efficacy

Prior	If observed pediatric SVR 12 = 95%			If observed pediatric SVR 12 = 90%		
	Bayesian Estimate (95% Cred. Int.)	Post. Prob. SVR12 > 82%	Post. Prob. SVR12 > 90%	Bayesian Estimate (95% Cred. Int.)	Post. Prob. SVR12 > 82%	Post. Prob. SVR12 > 90%
Skeptical	80.6 (70.3, 88.6)	37.8%	0%	76.3 (65.6, 85.2)	11.5%	0%
100% adult	95.3 (89.2, 98.6)	>99.9%	95.9%	91.5 (84.0, 96.3)	99.2%	67.4%
50%/50% mixture	95.3 (89.2, 98.6)	>99.9%	95.9%	91.5 (83.8, 96.8)	99.0%	67.2%
Non-informative	94.5 (85.7, 98.7)	99.5%	87.1%	88.3 (77.3, 95.3)	88.5%	34.7%

Case Example 2

- KANUMA (sebelipase alfa) – indicated to treat patients with Lysosomal Acid Lipase (LAL) deficiency. Approved in 2015
- **Wolman Disease**
  - One form of LAL
  - Infantile onset, homogeneous in its phenotype, highly progressive, fatal within the first six months of life. The estimated prevalence is approximately 1:500,000
- **Study Design**
  - Phase 1/2, multinational, open-label, single arm, N=9
  - Natural history study, multinational, collected retrospectively from chart reviews, no intervention, N=21
  - Primary endpoint: survival

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125561s000lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125561Orig1s000StatR.pdf

Case Example 2 - continued

Considerations

- Extremely rare – nine patients were recruited in three years
- Impossible to have concurrent control
- Utilization of historical control is reasonable if:
  - Comparable to the trial population in terms of baseline and observational variables
  - Endpoint is objective
  - Large treatment effect
- Note that comparisons to historical control may not as reliable as comparisons to randomized control: potential selection bias, latent variables, very small sample size, etc.

Labeling Requirement

FDA Guidance for Industry:

Data submitted in response to a written request under the BPCA and assessments submitted in response to a PREA study requirement must be described in labeling whether findings are positive, negative, or inconclusive. Pediatric information in the labeling must not be false or misleading in any particular.

Conclusion

- Challenges in pediatric drug development exist
- Opportunities for statistician to take the lead through different stages of the drug development cycle
- Demonstration of substantial evidence is required
- Early interaction with the FDA are encouraged

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Reference

1. FDA. (1998). Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products.
2. FDA. (2019a). Inclusion of adolescent patients in adult oncology trial guidance.
3. FDA. (2019b). Pediatric HIV infection drug development guidance.
4. FDA. (2019c). Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling.
5. FDA. (2019d). Rare Diseases Common Issues in Drug Development Draft Guidance.
6. FDA. (2019e). Rare Diseases Natural History Studies for Drug Development Draft Guidance.
7. ICH. (2000). Clinical Investigation of Medical Products in the Pediatric Population E11.
8. ICH. (2017a). Addendum to ICH E11: Clinical Investigation of Medical Products in the Pediatric Population E11(R1).
9. ICH. (2017b). General Principles for Planning and Design of Multi-Regional Clinical Trials E17.
10. Dunne, J., Rodriguez, W. J., Murphy, M. D., Beasley, B. N., Burckart, G. J., Filie, J. D., . . . Yao, L. P. (2011). Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics, 128*(5), e1242-1249. doi:10.1542/peds.2010-3487
11. Woodcock, J., & LaVange, L. M. (2017). Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *377*(1), 62-70. doi:10.1056/NEJMra1510062

Thank You!