FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Value of Pharmacokinetics in Pediatric Clinical Development

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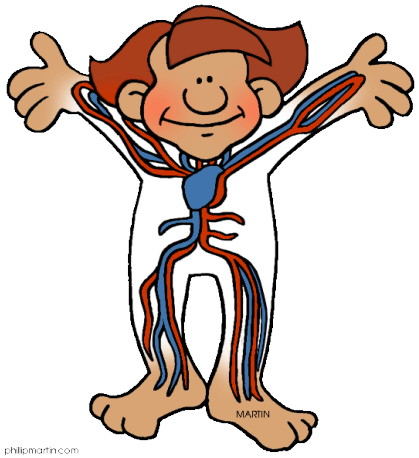
Disclaimer:
1. I have no conflict of interest to report.
2. The views presented here are my personal.

Outline

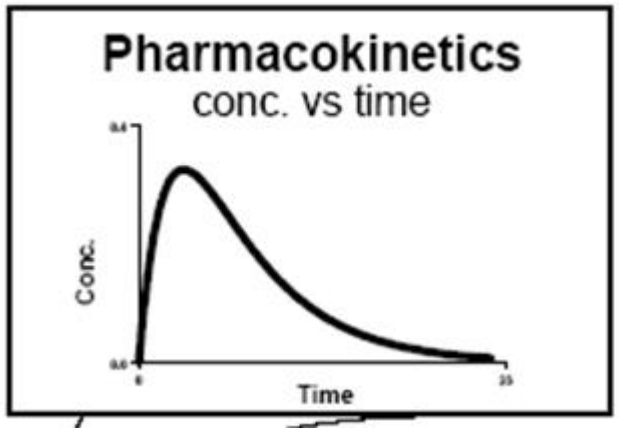
- **Introduction**
  - Pharmacokinetics (PK)
  - Characterization of pediatric PK
- **Value of PK in Pediatric Clinical Development**
  - Overview
  - Research and policy development
  - Pediatric clinical development cases
    - Efficacy extrapolation
    - Pediatric dose selection/determination
    - Clinical trial design
- **Take Home Message**

Pharmacokinetics

- Pharmacokinetics (**PK**): refers to the movement of drug into, through, and out of the body – the time course of its Absorption, Distribution, Metabolism, and Excretion (ADME).



The PK profile reflects:
- Patient characteristics
- Formulation features
- Chemical and physical properties of the drug



The PK links to clinical outcomes:
- Effectiveness
- Adverse events

Characterization of PK in Pediatrics

- PK features
- Patient age difference
- Formulation
- Clinical relevant exposure/PK variables
- ……..

Potential Changes in pediatric PK:

- Exposure
- Shape of PK profile change

Approaches for charactering PK in pediatrics:

- A PK study with intensive sampling
- Sparse PK sampling in pediatric patients
- Modeling and simulation (e.g., Pop-PK)

Value of PK in Pediatric Clinical Development

Drug Development

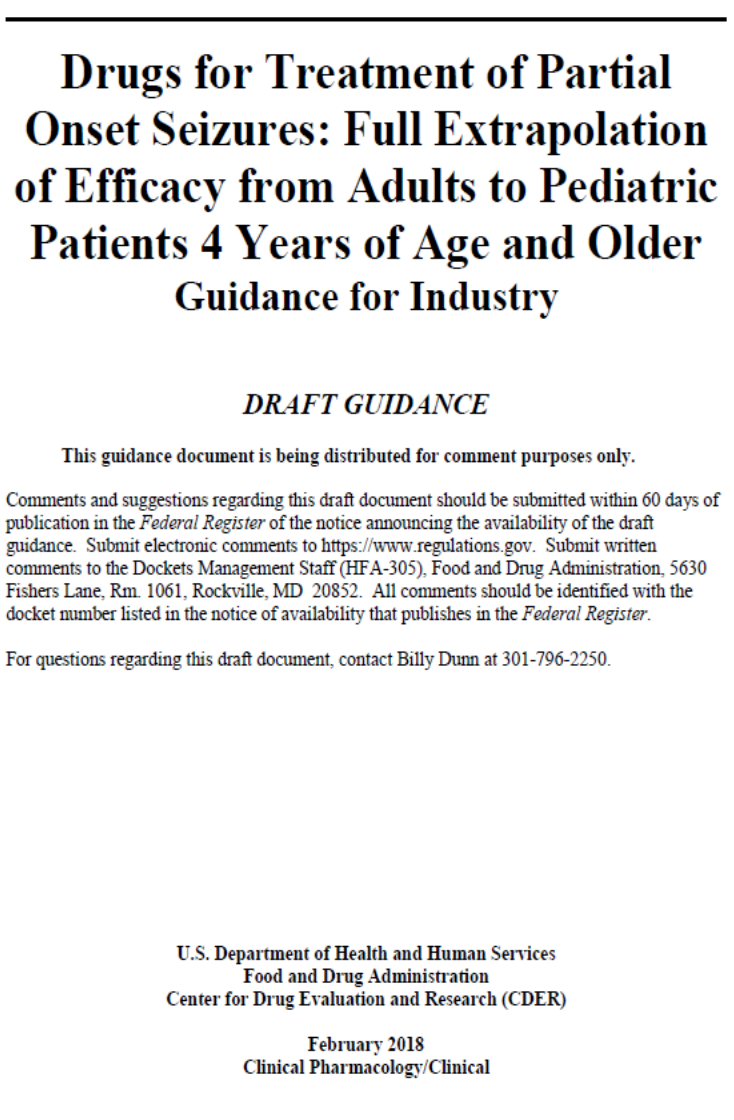
- Efficacy Extrapolation based on PK-Matching
- Dose Optimization using PK Information.
- Clinical Trial Design based on PK in Pediatrics.

Research and Policy Development

- Efficacy Extrapolation
- Joint Efficacy and Safety Trial with adults

Policy Development

- Efficacy extrapolation:
  - Basis for extrapolation
    - Similar progression of disease
    - Similar response of disease to treatment
    - Similar exposure-response relationship
  - ***Role of PK***
    - PK should be obtained from an adequately designed PK and tolerability study in which single and /or multiple doses of the investigational drug are administered in patients 4 to 16 years of age.
    - PK data should be sued to determine pediatric dosage and regimens based on PK-matching.



Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Billy Dunn at 301-796-2250.

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Extrapolation in Subgroups of ADHD Pediatric Patients

- Sponsors are highly encouraged to discuss their development strategy with the Agency during the Pre-IND stage. Some of the factors that should be considered to allow the extrapolation include:
  - The active ingredient of the 505(b)(2) product should only be methylphenidate or amphetamine.
  - The 505(b)(2) product should be given in the morning and target a duration of 12 hours or less.
  - ***Shape of the pharmacokinetic profile of the active moiety(ies) of the 505(b)(2) product must be similar across children, adolescents, and adults.***
  - The approved patient population of the listed drug should include children, adolescents, and adults. The dose for each patient population should be clearly defined.
  - An adequate bridging must be established between the 505(b)(2) product and the listed drug, such that the dose of the 505(b)(2) product in each patient population can be reliably derived.
  - Patients ages 4 and 5 years should be included in clinical trials. Although it is reasonable to extrapolate efficacy from older children to 4- and 5-year-old children, clinical trial data is necessary to compare the safety profile in this population to what is known about the listed drug.

Efficacy can be extrapolated from children to adolescents and adults with ADHD.

*: Hao Zhu. Extrapolation of Efficacy and Safety Findings from Children to Adolescents for CNS Stimulant 505 b(2) Products. ASCP Annual Meeting 2018.

Efficacy Extrapolation in Pediatric Development

Partial Onset Seizure in Pediatric Patients > 4 Years

Drug Name	Indication	Approaches to Support Pediatric Indication	Role of PK
Eslicarbazepine	Partial onset seizure in patients > 4 years	Extrapolation	Bridging efficacy and deriving pediatric dosing
Lacosamide	Partial onset seizure in patients > 4 years	Extrapolation	Bridging efficacy and deriving pediatric dosing
Pregabalin	Partial onset seizure in patients > 4 years	Extrapolation	Bridging efficacy and deriving pediatric dosing
Brivaracetam	Partial onset seizure in patients > 4 years	Extrapolation	Bridging efficacy and deriving pediatric dosing

Pediatric Dose Selection – Case Study (1)

- Drug X (A recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNFα)) is indicated for the treatment of Hidradenitis suppurativa (HS).
- HS is a rare disease in pediatric patients, where the prevalence is 0.002%, 0.027%, and 0.114% in patients < 9 years, 10-14 years, and 15-17 years.
- FDA expanded the adalimumab dosing regimen to adolescent HS patients 12 years and older, weighing at least 30 kg without additional clinical data in adolescent HS patients without clinical trials.

Pediatric Dose Selection – Case Study (2)

- Dosing regimen in patients > 12 years was determined through M&S relying on **PK-matching** with other patient populations (e.g. adults).
  - Pop-PK model with > 500 pediatric patients (other diseases) + > 3000 adults. Simulation was conducted to test alternative dosing regimens.

Body Weight of Adolescent HS Patients (12 years and older)	Recommended Dosing regimens
30 kg (66 lbs) to < 60 kg (132 lbs)	• 80 mg initially on Day 1 • 40 mg on Day 8 and subsequent doses: 40 mg every other week
≥ 60 kg (132 lbs)	• 160 mg initially on Day 1; and • 80 mg on Day 15 • 40 mg on Day 29 and subsequent doses: 40 mg every week

Dose Determination

Examples from Application of Animal Rule

Drug Name	Indication	Approval Basis for Pediatric Use	Role of PK
Raxibacumab	Treatment and prophylaxis of inhalational anthrax	Animal study + Extrapolation	M&S to predict exposure in pediatric patients and to match exposure in adults receiving 40 mg/kg.
Tecovirimat	Treatment of human smallpox disease	Animal study + Extrapolation	M7S to predict exposure in pediatric patients and to match exposure in adults receiving 600 mg BID

Clinical Trial Design

Case study: Aripiprazole is an atypical antipsychotic.

Role of PK

PK in pediatric patients 10-17 years showed similar exposures of the major active moieties as compared to adults

Determine dose ranges for pediatric clinical trials

Pediatric Clinical Trials

- Schizophrenia: 6-week, placebo-controlled clinical trial in 202 pediatric patients 13-17 years
- Bipolar I disorder: 4-week, placebo-controlled clinical trial in 197 pediatric patients 10-17 years
- Irritability associated with autistic disorder: two 8-week, placebo-controlled clinical trials in 212 pediatric patients 6-17 years
- Tourette's disorder: One 8-week (7-17 years) and one 10-week (6-18 years).

Take Home Message

- PK in pediatric patients can be characterized in different ways
  - Intensive PK sampling in dedicated studies.
  - Sparse PK sampling
  - Modeling and simulation.
- PK information is critical to inform pediatric drug development:
  - To support policy development
  - To facilitate pediatric clinical development
    - Efficacy extrapolation
    - Dose selection/determination
    - Clinical trial design

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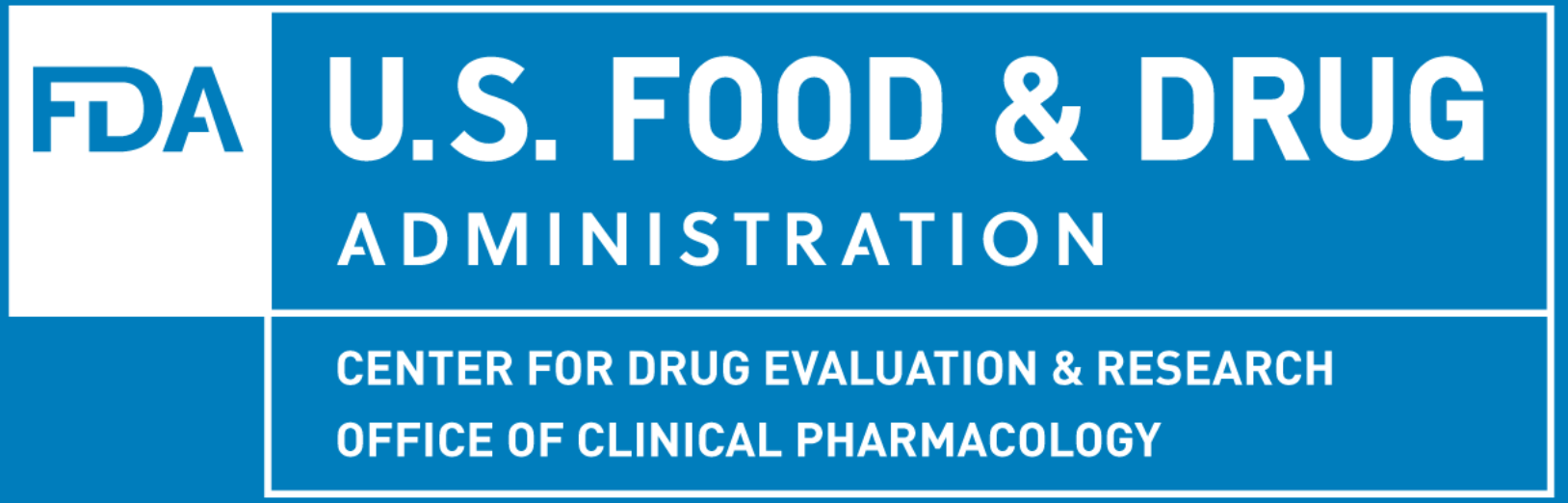
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