

Application of Ontogeny in MIDD for Pediatrics

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

Outline

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 - Challenges in pediatric drug development
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 - MIDD
 - MIDD under PDUFA VI
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 - To understand ontogeny through submissions
 - To include ontogeny to support dose selection
 - To include ontogeny to support product approval
- **Take Home Message**

Challenges in Pediatric Drug Development



- Challenges:
 - Time delay between adult approval and inclusion of pediatric information in labeling is still substantial.
 - Specific issues in pediatric patients:
 - Ontogeny
 - Pediatric-specific diseases.
- Effort:
 - Continuous investment.
 - Innovative approaches in pediatric drug development.

- MIDD: Model Informed Drug Development*
(Historically, model-aided drug development, model-based drug development)
 - Application of a wide range of quantitative models in drug development to facilitate decision making process.
 - It has been used to support dose selection/optimization, supportive evidence for efficacy, clinical trial design, and policy development.

*: [Wang Y](#)¹, [Zhu H](#)¹, [Madabushi R](#)¹, [Liu Q](#)¹, [Huang SM](#)¹, [Zineh I](#)¹. Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations. [Clin Pharmacol Ther](#). 2019 Apr;105(4):899-911. doi: 10.1002/cpt.1363.

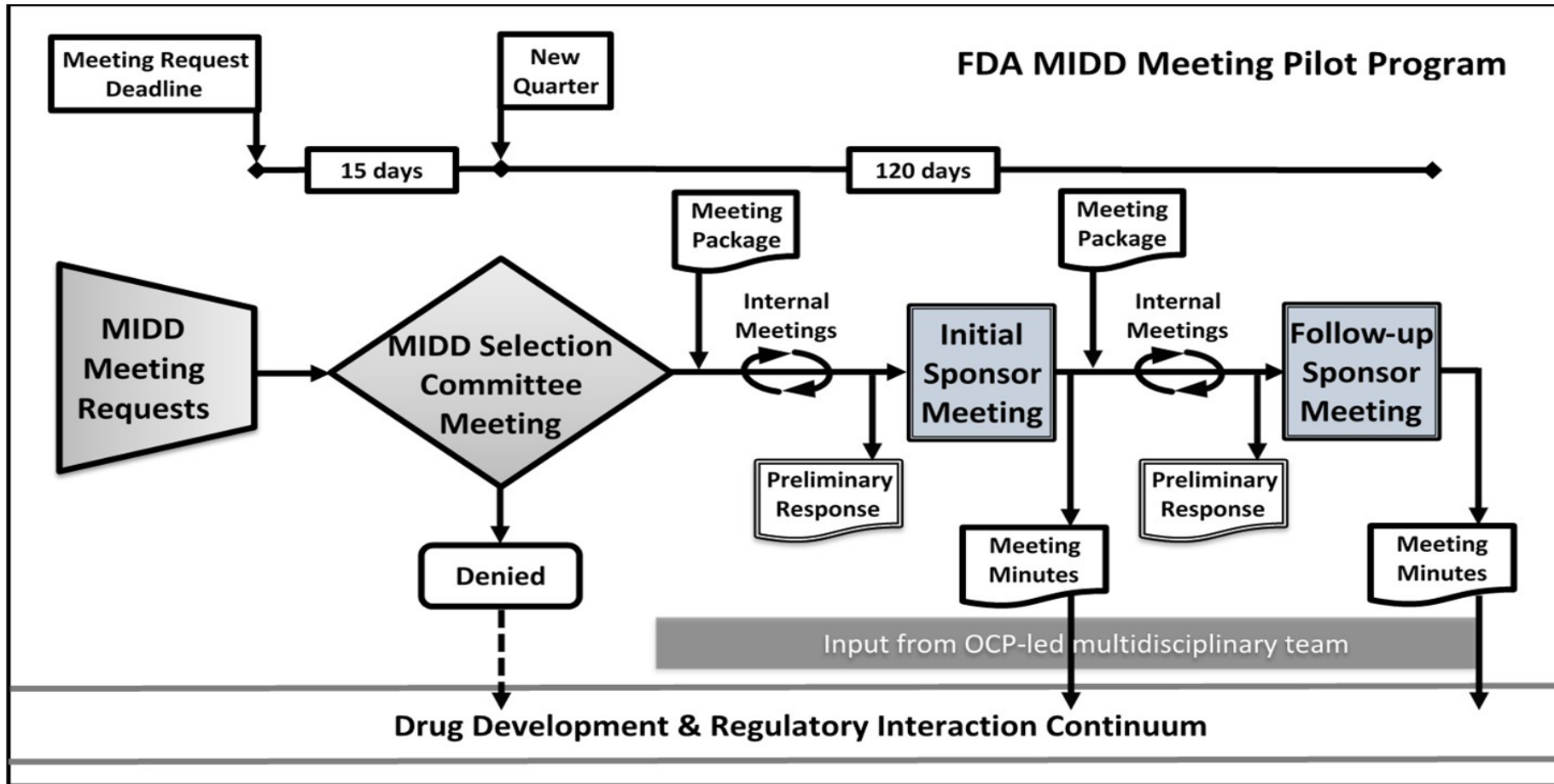
MIDD Programs Under PDUFA VI



- MIDD effort under Prescription Drug User Fee Act (PDUFA) VI *:
 - MIDD pilot meeting program: To promote early interaction between the drug developers and FDA on key issues at different stages during clinical development.
 - MIDD related workshops: To facilitate a broad discussion on best practice and experience exchange on MIDD among all stake holders.
 - The first workshop in 2018 highlighted MIDD in dose selection and trial design for oncology products.
 - The second workshop in 2019 focuses on PBPK modeling
 - Update MIDD related guidance: Pop-PK guidance, E-R guidance, etc.

: Hao Zhu, Shiew Mei Huang, Raj Madabushi, David Strauss, Yaning Wang, Issam Zineh. Model-informed Drug Development: A Regulatory Perspective on Progress. CPT (to be published)

MIDD Pilot Meeting Program



*: Rajanikanth Madabushi¹, Jessica M. Benjamin¹, Renmeet Grewal¹, Michael A. Pacanowski¹, David G. Strauss¹, Yaning Wang¹, Hao Zhu¹, Issam Zineh¹ The US Food and Drug Administration’s Model-Informed Drug Development Meeting Pilot Program: Early Experience and Impact. CPT (To be published)

Fit for Purpose Program

- Fit for Purpose Program (FFP)
 - To provide a mechanism for evaluation and regulatory acceptance of dynamic drug development tools intended to broadly enable drug development.

Disease Areas	Submitters	Tool	Trial Component
Alzheimer’s Disease	CAMD	Disease Model: Placebo/disease progression	Demographics Drop out
Multiple	Janssen and Novartis	Statistical Methods: MPC-Mod	Dose-finding

Ref: <https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative>.

Case Studies

- Case 1: To understand ontogeny in pediatric patients based on NDA data.
- Case 2: Ontogeny information is applied to support dose selection in pediatric patients < 2 years.
- Case 3: Ontogeny information is used to support product approval in pediatric patients < 2 years without clinical trial data.

Case 1: Gadovist[®] and Dotarem[®]



- **Compound:** Gadolinium-based MRI contrast agents
- **Approved Indications:** for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
- **ADME Features:**
 - Gadovist[®]: approximately 99% of the dose can be recovered in urine in 6 hours.
 - Dotarem[®]: approximately 85-92% of the dose can be recovered in urine in 48 hours.

Ref: Dr. Yaning Wang. Comparison of Various Renal Function Models in Neonates. ASCPT 2019.

Clinical Data

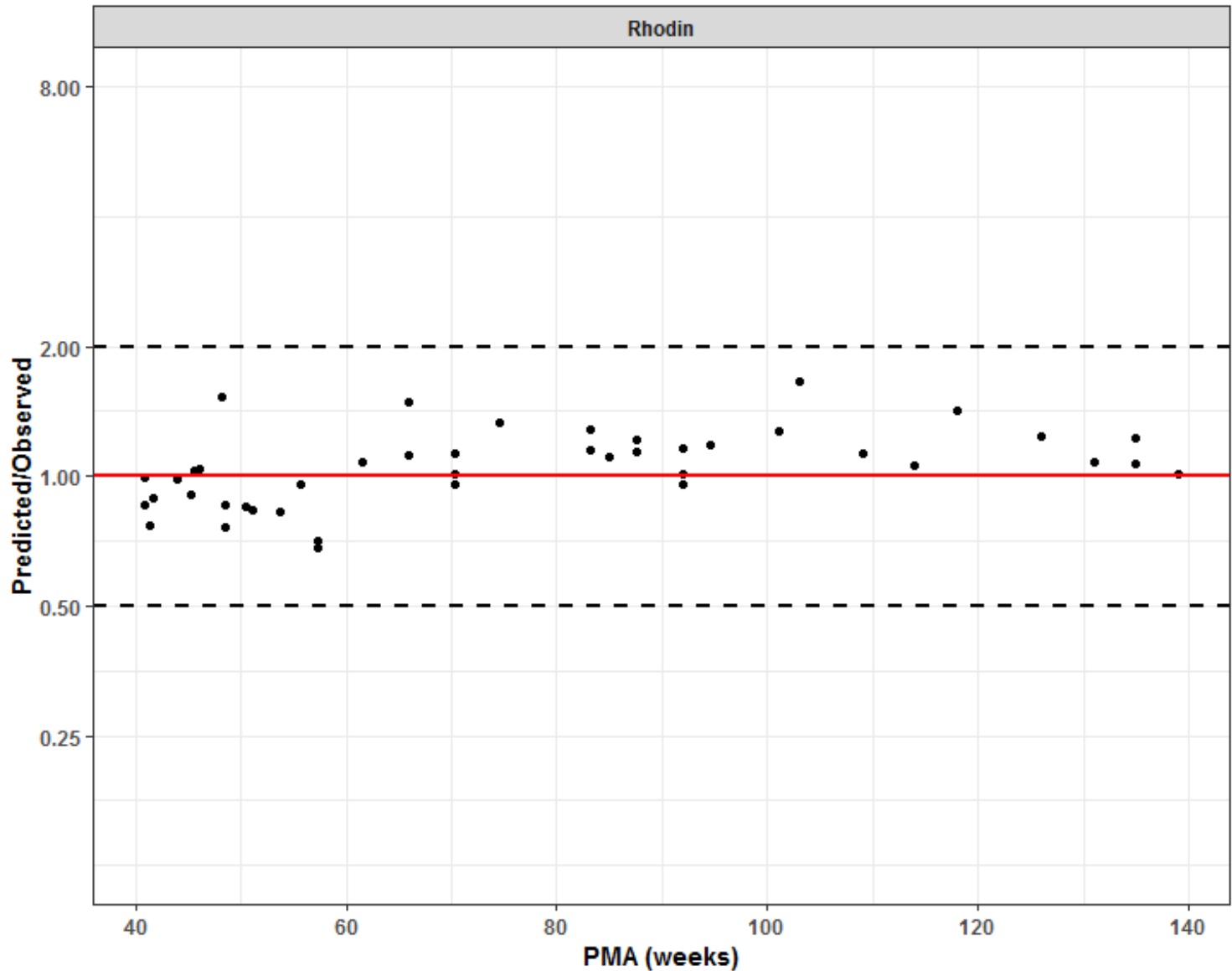
- **Gadavist :**

- term newborns.
- N=43 (38 subjects >1 months, 5 subjects < 1 months)
- Sparse Sampling scheme: 3 blood samples per subject; one during each time window (15 min to 60 min, 2.0 hours to 4.0 hours and 6.0 hours to 8.0 hours post-injection)

- **Dotarem:**

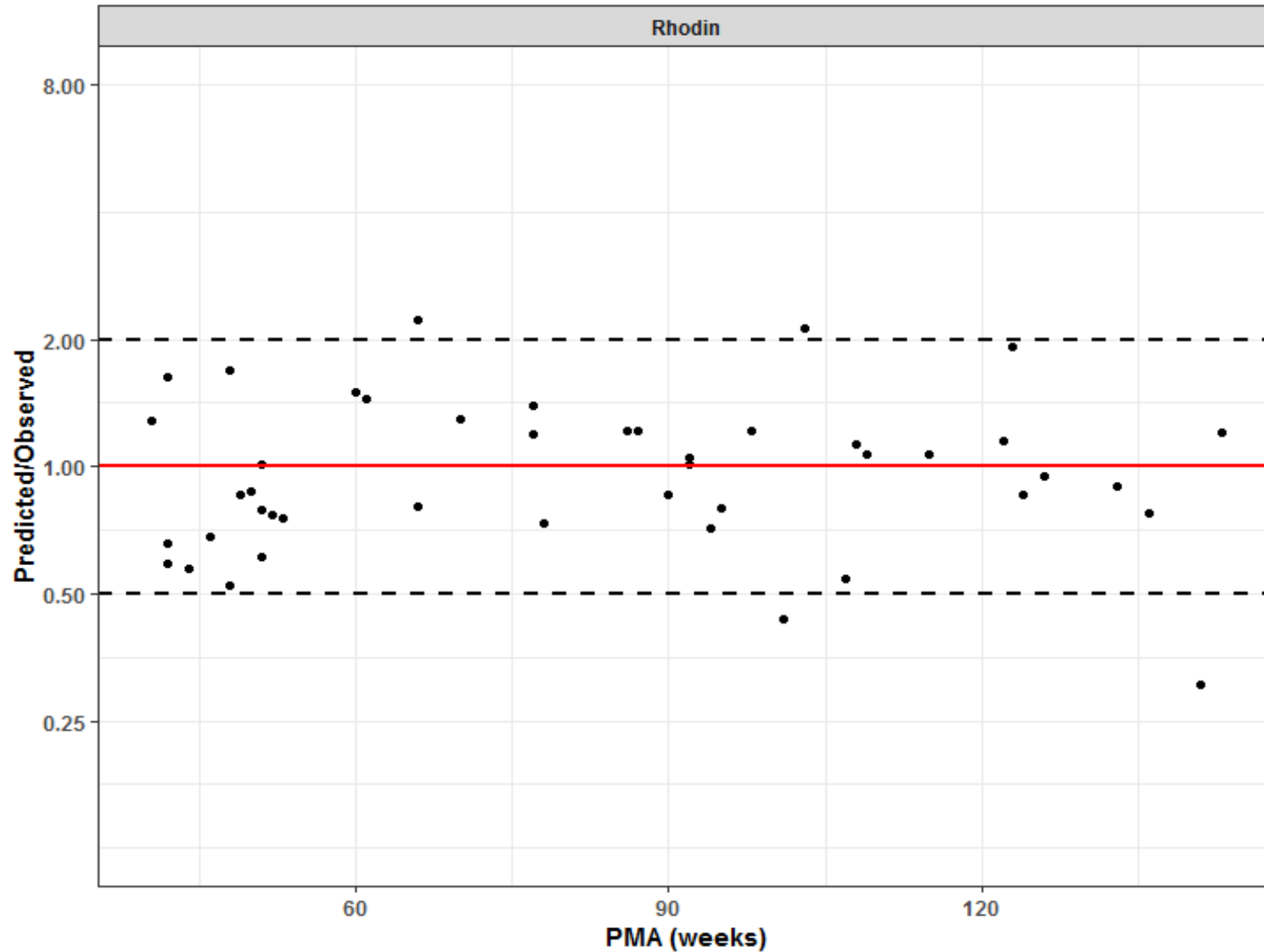
- term newborns.
- N=45 (40 subjects >1 months, 5 subjects < 1 months)
- Sparse Sampling scheme: 3 blood samples per subject; one during each time window (10 min to 60 min, 2.0 hours to 4.0 hours and 6.0 hours to 8.0 hours post-injection)

Understand eGFR using Gadavist[®] Data



PMA: Postmenstrual Age

Understand eGFT using Dotarem[®] Data



PMA: Postmenstrual Age

Case 2: A MRI Contrast Agent

- Compound: MRI contrast agent.
- Initial approved indication:
MRI of CNS in adults and pediatric patients (>2 year), to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues.
- Dosing:
 - 0.2 mL/kg (0.1 mmol/kg)

*: Acknowledgement: Drs. Justin Earp, Yaning Wang, Nam Atiqur Rahman

ADME Features

- Elimination:
 - Renal elimination is the primary route (~ 95%).
 - Hepatic elimination accounts for less than 5% of total clearance.
 - Renal clearance is similar to that of substances that are subject to glomerular filtration.
- Biotransformation: No detectable biotransformation.
- Organ dysfunction studies:
 - Renal impairment: Significantly delay the drug elimination.
 - Hepatic impairment: little effect on PK.

Clinical Evidence for Initial Indication



- Efficacy and Safety Trials:
 - Adult indication: 2 efficacy and safety trials. Consistent improvement across all independent readers with the contrast agent.
 - Pediatric patients (2-17 years of age): Similar findings to adults
- Pediatric PK trial (2-16 years of age)
- PK in adults

Information to Support Indication in Pediatric Patients < 2 Years



- No PK study in pediatric patients < 2 years of age.
- Population PK M&S was conducted based on PK collected in adults and pediatric patients > 2 years to derive PK in pediatric patients < 2 years.
 - Two compartment model
 - V_1 and $V_2 \sim (WT/WT_{sd})^{0.96}$, $CL \sim (WT/WT_{sd})^{0.68} * (CRCL/CRCL_{sd})^{0.29}$
 - PK parameters are consistent with the physiology of the drug.

M&S in Pediatric Patients < 2 Years

- Simulation in pediatric patients < 2 years:
 - Maturation of GFR was considered to be synonymous with CRCL.
 - CL is described as a function of WT and AGE by Rhodin et al. * (using 923 subjects from neonates to adults).
- Simulation results:
 - Support body weight adjusted dosing in pediatric patients < 2 years of age.
 - 0.1 ~ 0.2 mL/kg (0.05 ~ 0.1 mmol/kg) is a reasonable dose in this patient population

* Ref: [Rhodin MM](#) et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. [Pediatr Nephrol](#). 2009 Jan;24(1):67-76. doi: 10.1007/s00467-008-0997-5.

Addition Supporting Evidence

- Efficacy and safety study in pediatric patients < 2 years of age: (~ 90 subjects).
 - Two out of three readers reported improvement in reading the paired image setting across all endpoints.
 - Safety profile has been established in pediatric patients < 2 years of age.
- New Indication:
 - magnetic resonance imaging (MRI) of the central nervous system (CNS) in adults and pediatric patients (including term neonates), to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues.
 - Dosing: 0.1 – 0.2 mL/kg.

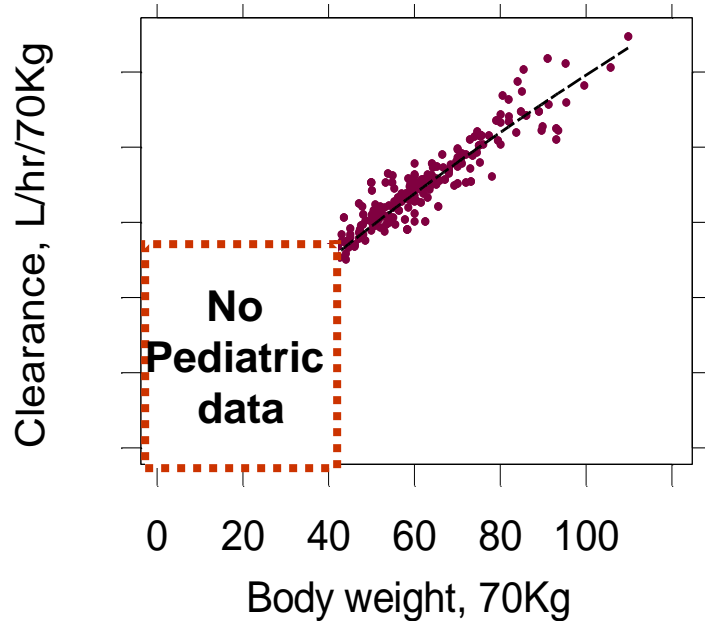
Case 3: Drug A

- Treatment of a life-threatening viral disease (public health emergency)
- Efficacy and Pharmacokinetic data from 200 adults
 - Age: 20-65 yrs; Weight: 40-110 Kg
- Target AUC established in adults
- Drug is cleared exclusively through renal route

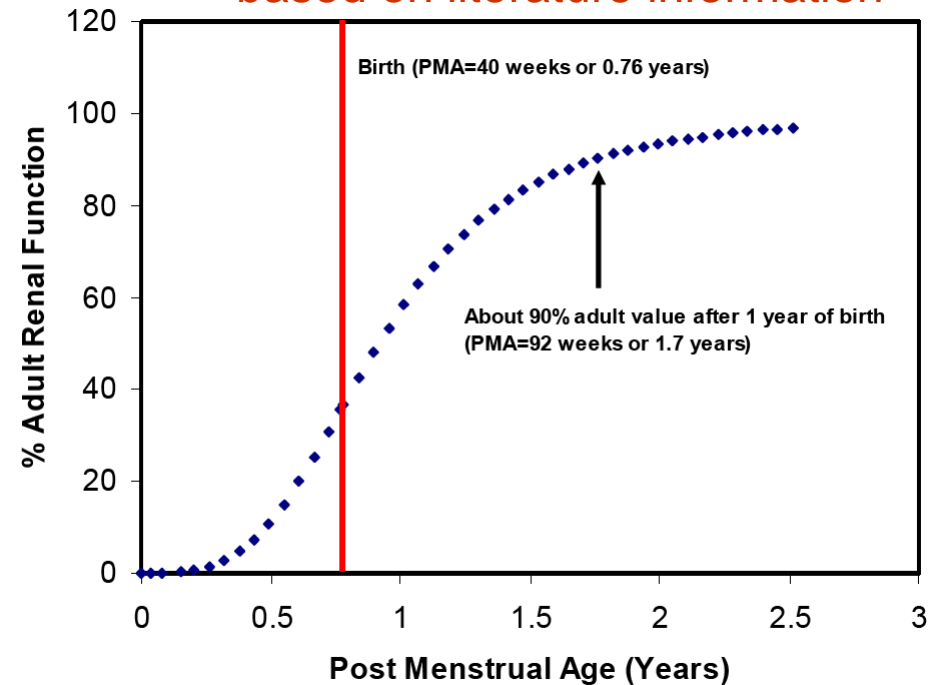
Adopted from Dr. Qi Liu's previous presentation

Allometry and Renal Function Maturation

Allometric model was used to fit data from adults



Renal function maturation was incorporated based on literature information



Rhodin et. al. (Pediatr Nephrol (2009) 24:67–76)

PK Prediction and Dose Selection in Pediatrics

Patients



- Simulations combining renal function maturation and allometry allowed reasonable estimation of clearance in pediatric patients
- Simulations were conducted to select a dosing regimen

Highlight of Case 3

In deriving pediatric dosing, modeling and simulations allowed us to ...

- Incorporate ontogeny information to account for organ function maturation
- Derive dosing recommendations for pediatrics in the absence of pediatric data

Take Home Message

- The quantitative information on ontogeny is critical for drug development in pediatric patients.
 - Evolving field
- MIDD related programs provide regulatory pathways to promote early interaction between drug/tool developers and FDA potentially allowing incorporation of the latest scientific findings (e.g., ontogeny-related findings) into pediatric drug development.

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