Destination PBPK in Pediatric Product Life Cycle Management: “Are we there yet?”

Nikunjkumar Patel, PhD

PQRI Workshop: MIDD Approaches in Pediatric Formulation Development
Feb 28-29, 2024
Virtual Event

Exponential growth in scientific knowledgebase for pediatric biopharmaceutics

Review of paediatric gastrointestinal physiology relevant to the absorption of orally administered medicines

Erik Wollmer [1], Anna-Lena Ungell [2], Jean-Marie Nicolas [3], Sandra Klein [4]

Current challenges and future perspectives in oral absorption research: An opinion of the UNGAP network

Zahari Vinarov [1], Bertil Abrahamsson [2], Per Artursson [3], Hannah Batchelor [4], Philippe Berben [5],

A mechanistic approach to understanding oral drug absorption in pediatrics: an overview of fundamentals

Nir Debotton [1], Arik Dahan [2]

Oral drug absorption in pediatrics: the intestinal wall, its developmental changes and current tools for predictions

Jean-Marie Nicolas [1], François Bouzom [1], Chanteux Hugues [1], Anna-Lena Ungell [1]

Biopharmaceutical considerations in paediatrics with a view to the evaluation of orally administered drug products – a PEARRL review

Mariana Guimarães [1], Marina Statelova [2], René Holm [3], Christos Reppas [2], Moira Symilllides [2], Maria Vertzoni [2], Nikoletta Fotaki [1]

Gastrointestinal Fluid Volumes in Pediatrics: A Retrospective MRI Study

Matthias Van der Veken [1], Michael Aertsen [2], Joachim Brouwers [1], Cordula Stillhart [3], Neil Parrott [4], Patrick Augustijns [1]

Ontogeny of oral drug absorption processes in children

Miriam G Mooij [1], Barbara A E de Koning, Mark L Huijsman, Saskia N de Wildt

Magnetic Resonance Imaging Quantification of Gastrointestinal Liquid Volumes and Distribution in the Gastrointestinal Tract of Children

Eleni Papadatou-Soulou [1], Julie Mason [1], Caron Parsons [2], Adam Oates [3], Manigandan Thyagarajan [3], Hannah Katharine Batchelor [1]

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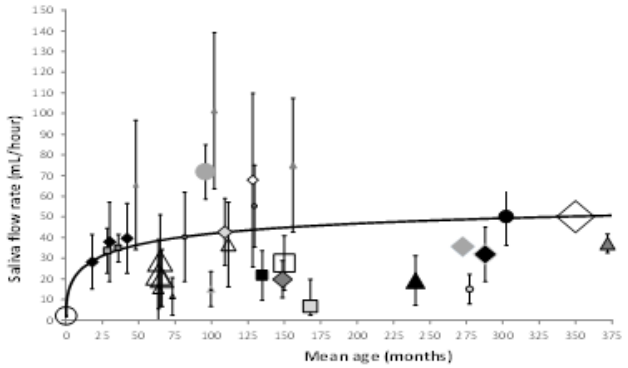
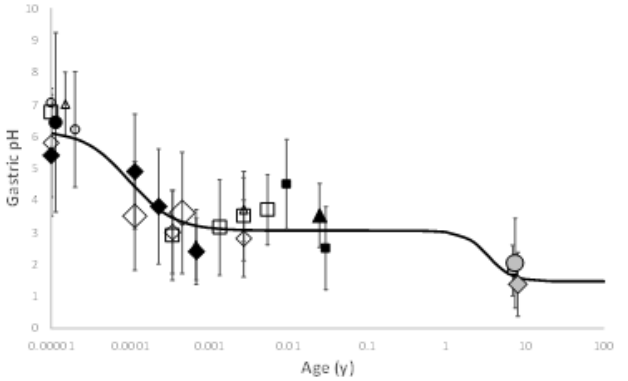
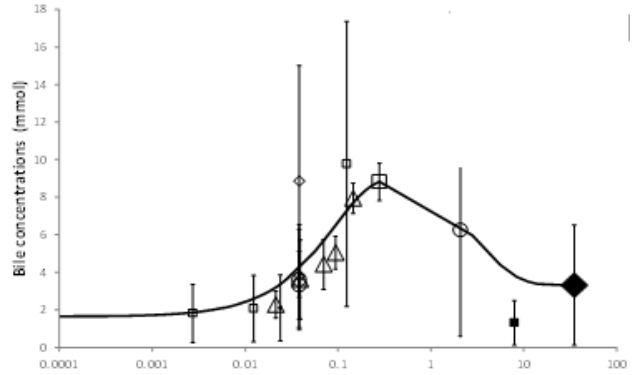
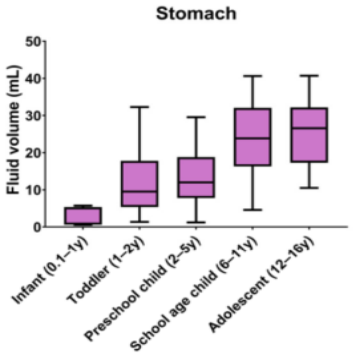
Pediatric GI Physiology Ontogenies

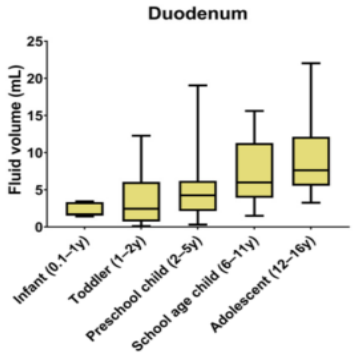


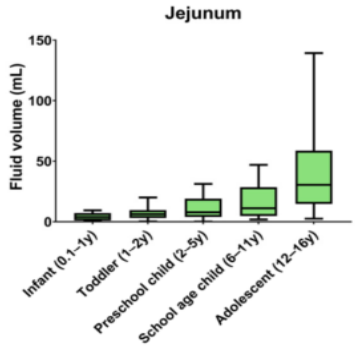


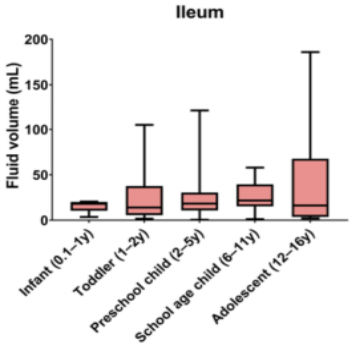


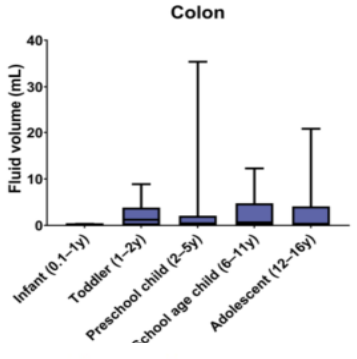
Johnson et al. 2018

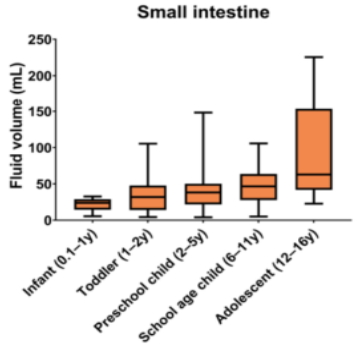


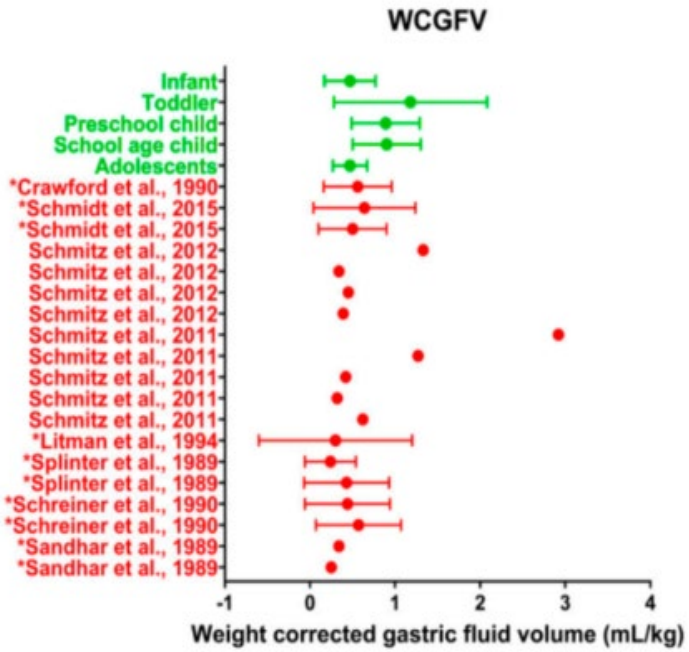




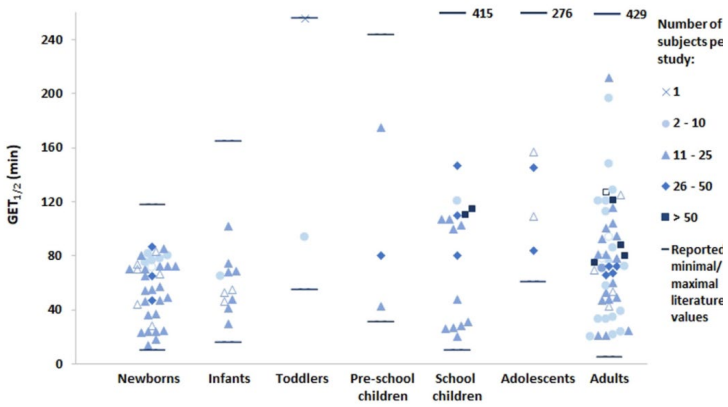




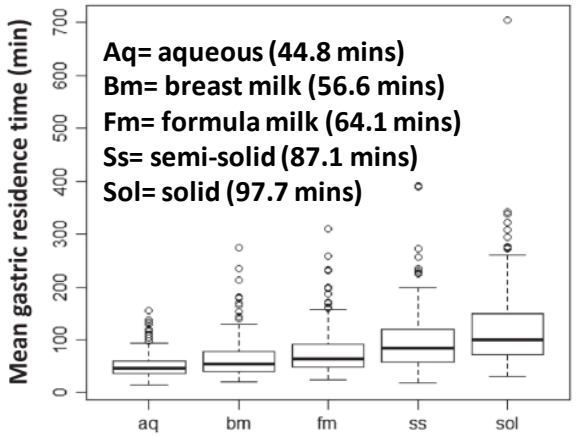




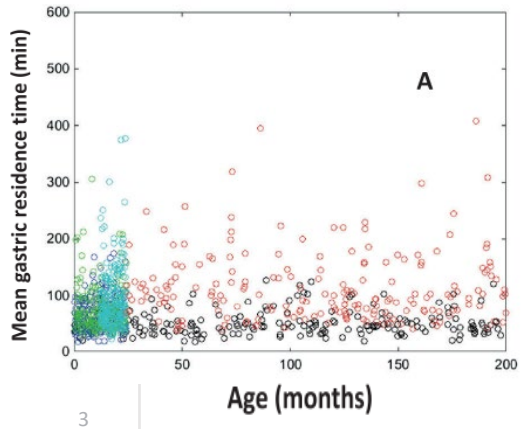
Van der Veken et al. 2022



Wolmer et al. 2022



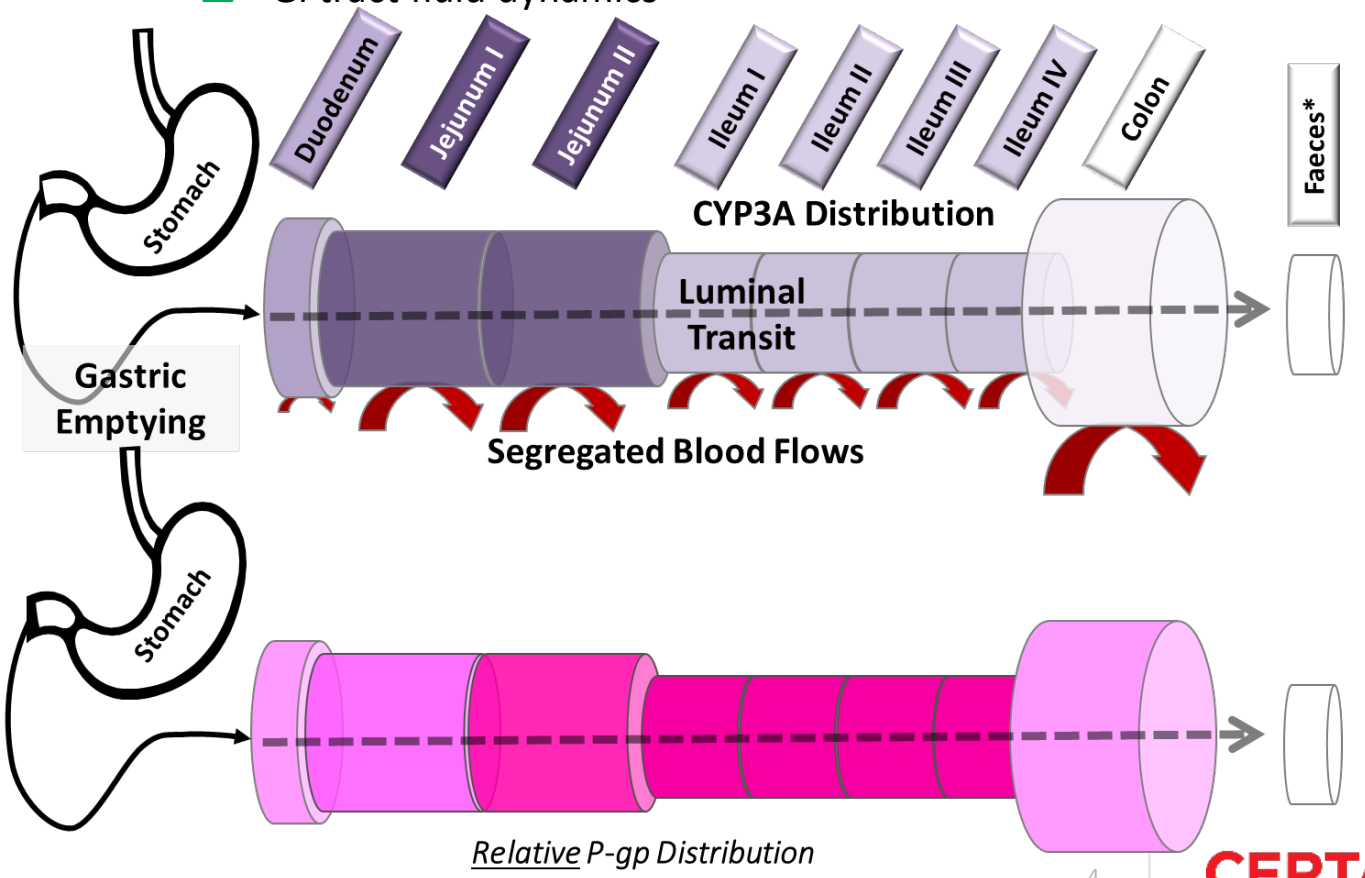
Bonner et al. 2015



Simcyp Pediatric ADAM - Advanced Dissolution, Absorption & Metabolism Model

Incorporated Pediatric physiology data

- ☑ Stomach volume
- ☑ Gastric emptying
  - ☑ No significant effect of age on mean gastric residence time
  - ☑ Food type effects significant
- ☑ Intestinal length/diameter
  - ☑ ↑ as function of age
  - ☑ Already in Simcyp
- ☑ Transit times
  - ☑ No change with age
- ☑ Permeability
  - ☑ Neonatal period of enhanced permeability to large hydrophilic molecules (prob. paracellular)
- ☑ pH
  - ☑ Gastric: ↑ in early postnatal period
- ☑ Intestinal CYP3A ontogeny
  - ☑ ↑ in expression and activity with age
  - ☑ Already in Simcyp
- ☑ Bile production and composition
- ☑ Salivary production and flow
  - ☑ Age related change
- ☑ Intestinal transporter ontogeny
  - ☑ Some information on P-gp
  - ☑ Little information on BCRP, MRP2
- ☑ GI tract fluid dynamics



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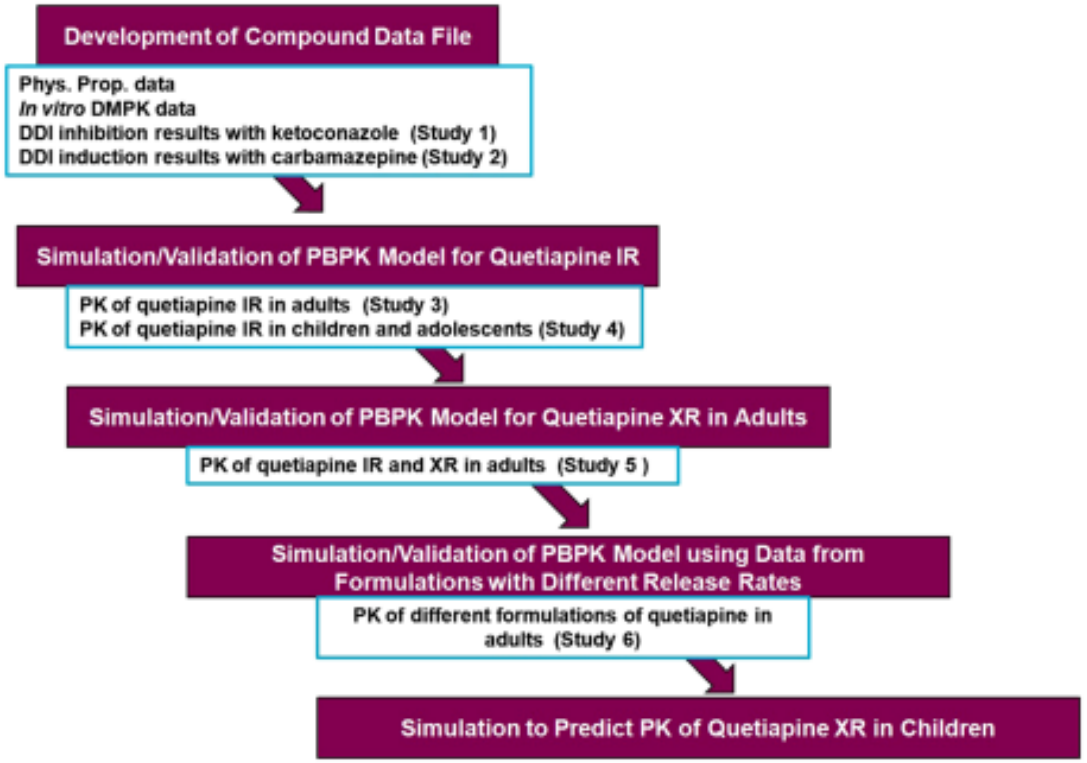
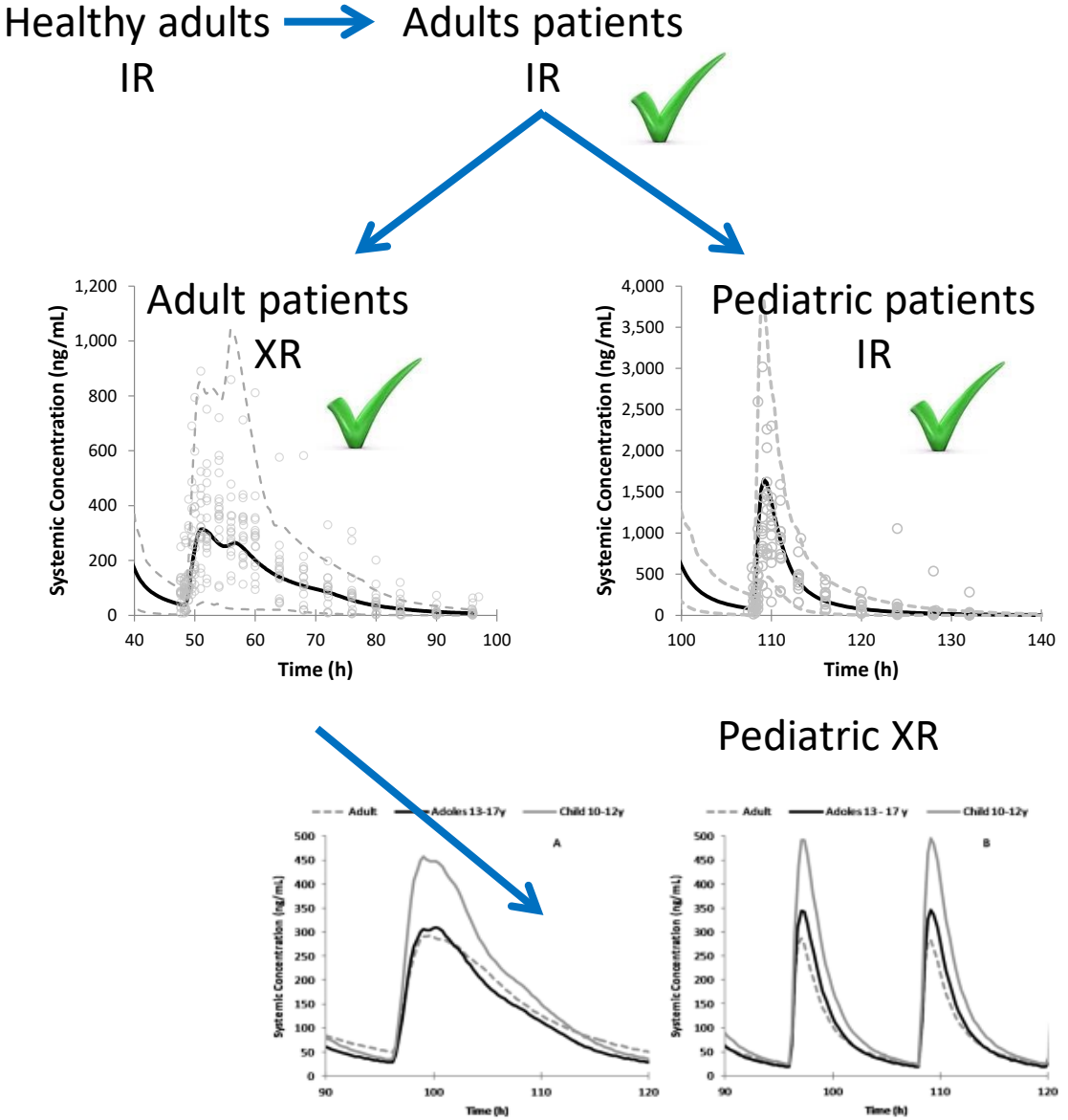
PBPK In Pediatric Product Assessment: Extended-Release formulation

Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

Trevor N Johnson [1], Diansong Zhou, Khanh H Bui





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PBPK In Pediatric Product Development: Modified Release formulation

Development and verification of an endogenous PBPK model to inform hydrocortisone replacement dosing in children and adults with cortisol deficiency

Jennifer J Bonner [1], Howard Burt [2], Trevor N Johnson [2], Martin J Whitaker [3], John Porter [4], Richard J Ross [3]

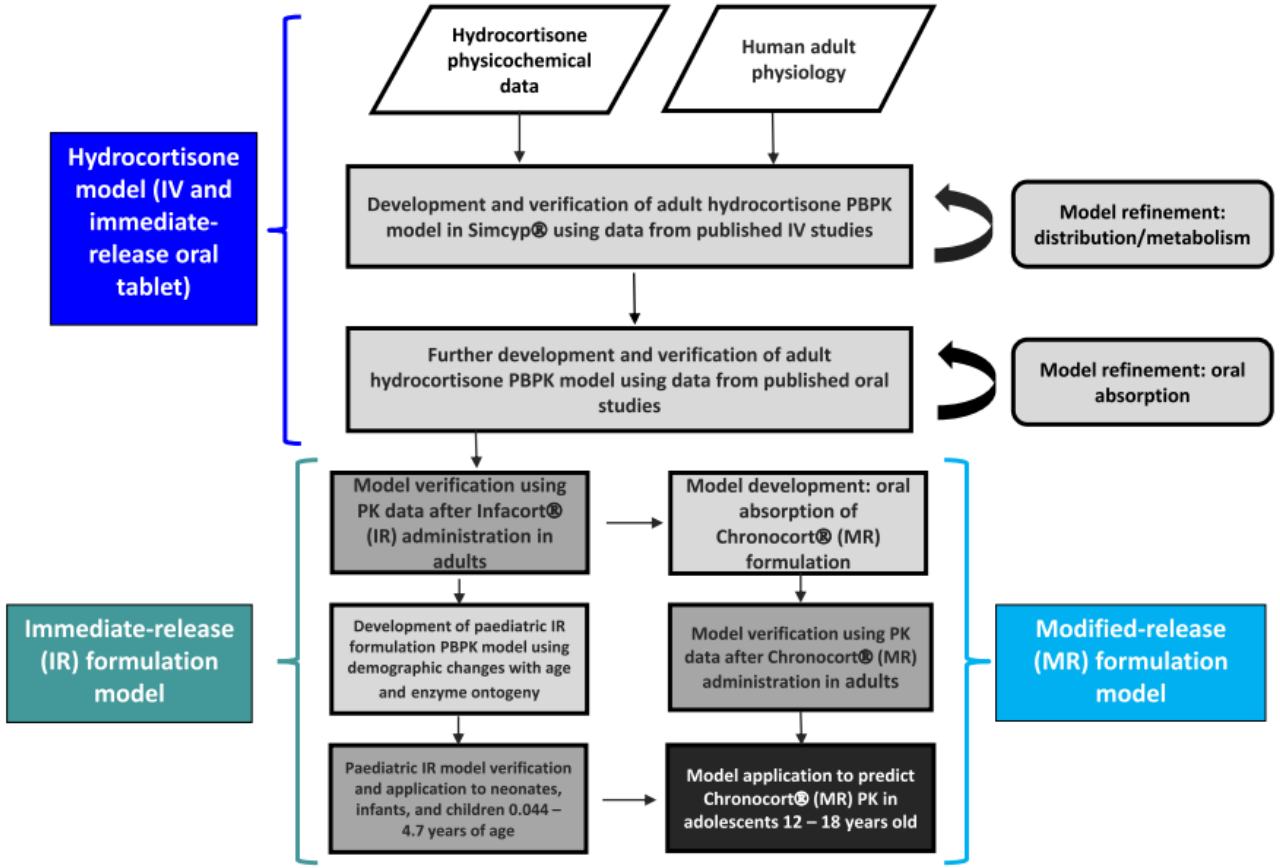
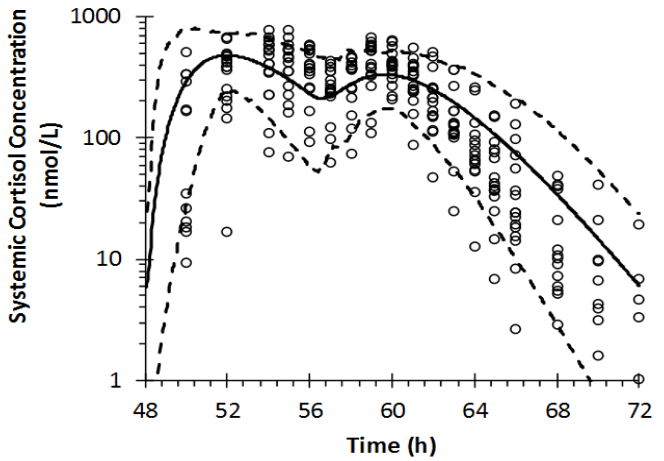
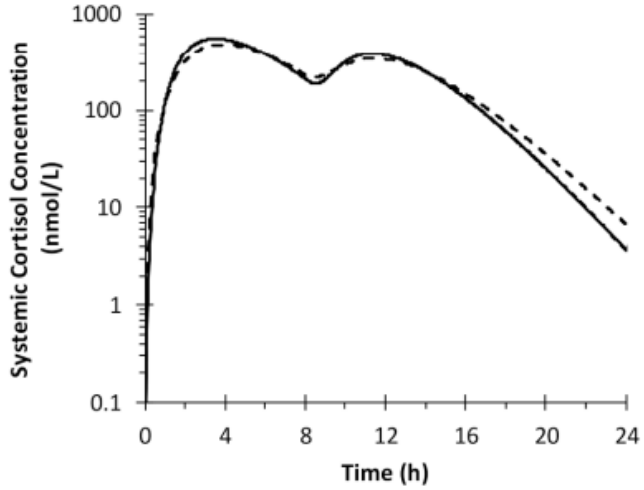


Fig. 1. Workflow of hydrocortisone model development, verification, and application



20mg evening, 10mg morning in adults



11.6 mg/m^2 evening, 5.8 mg/m^2 morning adolescents aged 12 to 18 years (solid line). Adults (dotted line).

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PBPK In Pediatric Product Development: Adult IR to Pediatric Suspension virtual BE

Physiologically Based Pharmacokinetic Model Development and Verification for Bioequivalence Testing of Bempedoic Acid Oral Suspension and Reference Tablet Formulation

Benny M Amore [1], Nikunjkumar Patel [2], Priya Batheja [1], Ian E Templeton [2], Hannah M Jones [2], Michael J Louie [1], Maurice G Emery [1]

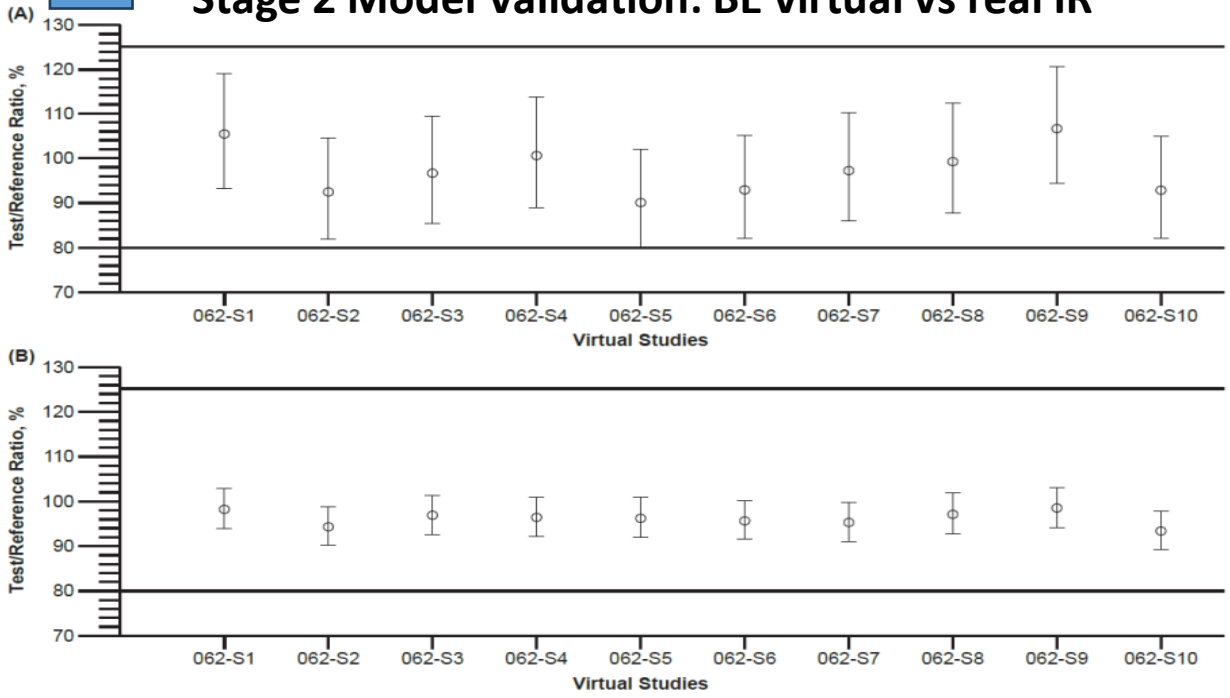
Stage 1 Model Validation: Adult IR SD/MD PK

Bempedoic Acid 180 mg Regimen	Clinical Study	Concomitant Treatment (No. Subjects)	Estimate	C_{max}, µg/mL	AUC_{inf} (Single Dose) or AUC_{24h} (Repeat Dose) [a], µg·h/mL
Single Dose	002	NA (N = 58)	Predicted	18.0 (2.60)	273 (102)
			Observed	13.5 (3.19)	225 (70.3)
			Pred/Obs Ratio	1.33	1.21
Repeat Dose (Steady-State)	003	Atorva80 (N = 12)	Predicted	24.5 (5.82)	267 (111)
			Observed	27.3 (6.98)	348 (95.7)
			Pred/Obs Ratio	0.90	0.77
		Simva40 (N = 12)	Predicted	23.8 (5.46)	260 (105)
			Observed	24.7 (6.99)	276 (64.5)
			Pred/Obs Ratio	0.96	0.94
		Prava80 (N = 12)	Predicted	25.1 (6.06)	274 (116)
			Observed	23.7 (5.59)	289 (106)
			Pred/Obs Ratio	1.06	0.95
		Rosuva40 (N = 12)	Predicted	24.3 (5.76)	265 (108)
			Observed	21.9 (9.60)	264 (129)
			Pred/Obs Ratio	1.11	1.01

Model Application: virtual BE Suspension vs Tablet

Virtual Study Design	Parameter	Pilot Scale Suspension GM Estimate (%CV)	Commercial Tablet GM Estimate (%CV)	Test/Reference Ratio (90% CI)
Crossover	C_{max}, µg/mL	19.6 (11.5)	19.6 (12.7)	99.7% (96.1–103)
	t_{max}, h	1.57 (38.0)	1.56 (38.3)	nc
	AUC_{last}, µg·h/mL	313 (33.2)	313 (33.2)	100% (90.6–110)
	AUC_{inf}, µg·h/mL	329 (39.2)	329 (39.2)	100% (89.1–112)
Parallel	C_{max}, µg/mL	17.2 (13.0)	17.8 (16.8)	96.9% (92.6–101)
	t_{max}, h	1.85 (34.2)	1.68 (36.3)	nc
	AUC_{last}, µg·h/mL	259 (38.8)	264 (41.4)	98.2% (87.3–111)
	AUC_{inf}, µg·h/mL	270 (42.6)	274 (45.9)	98.4% (86.4–112)

Stage 2 Model Validation: BE virtual vs real IR



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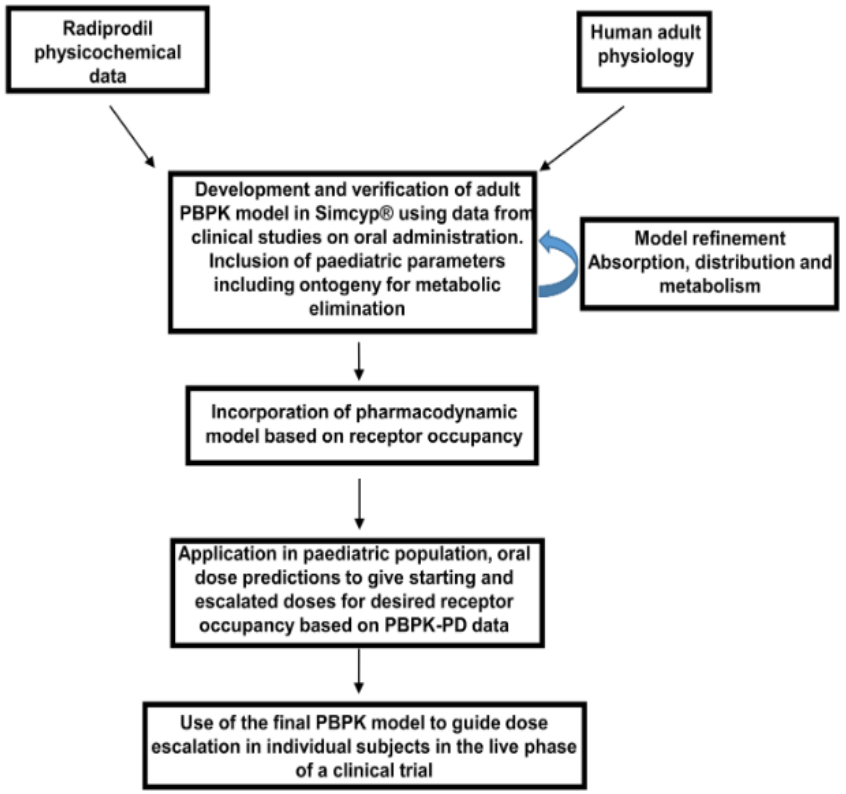
PBPK In Pediatric Product Development: IR to Suspension Dose finding/escalation

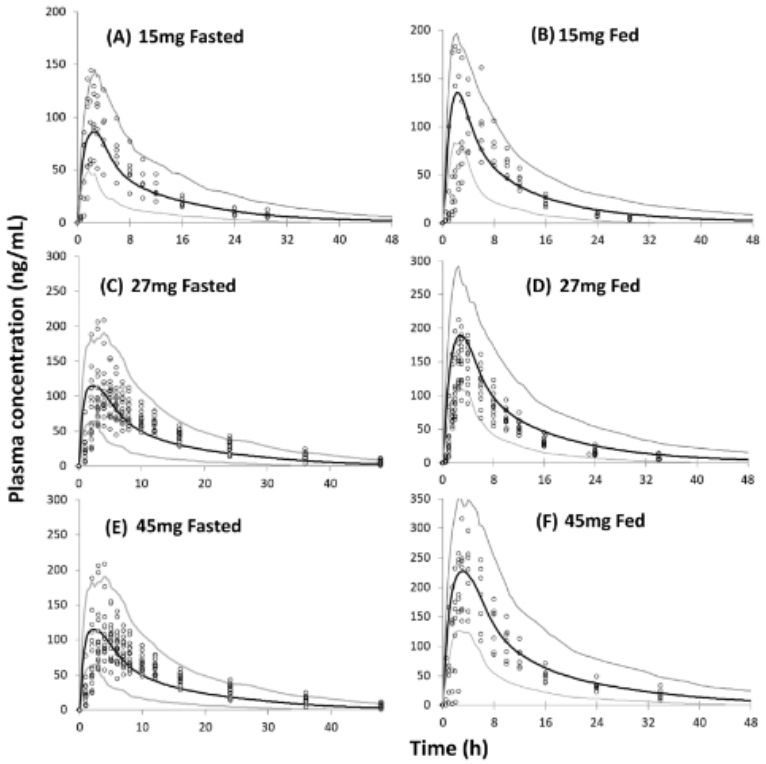
Use of a physiologically based pharmacokinetic–pharmacodynamic model for initial dose prediction and escalation during a paediatric clinical trial

Trevor N Johnson [1], Khaled Abduljalil [1], Jean-Marie Nicolas [2], Pierandrea Muglia [2], Hugues Chanteux [2], Johan Nicolai [2], Eric Gillent [2], Miranda Cornet [2], David Sciberras [2]

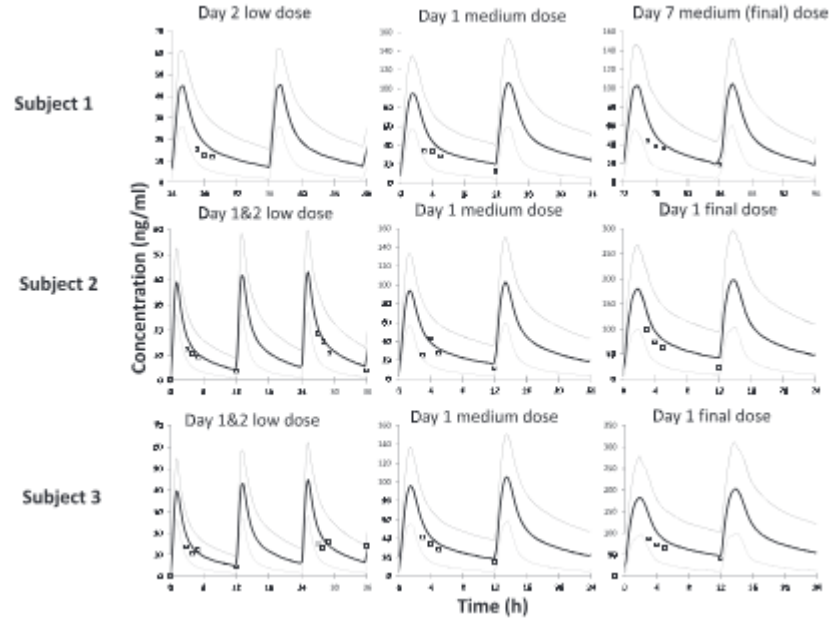
The PBPK model was used to determine initial doses with age and to guide dose escalation for pediatric individual subjects in the live phase of a clinical trial using suspension formulation, predicted and observed data was in close agreement.



Adult Immediate Release



Pediatric Suspension



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Are we there yet?

……Almost there…

- Collaborative efforts between academia, industry and PBPK model developers are producing relevant and richer physiological data to parametrize developmental changes in absorption related processes in PBPK models.
- Enriched, user-friendly PBPK modeling platforms supported with ontogeny databases are widely and easily available.
- Increased utilization of pediatric PBPK models in pediatric product development is allowing efficient regulatory pathways.
- Peer-reviewed publications of case examples by academia, model developers, industry and regulators are disseminating scientifically scrutinized research for other scientists to learn, deploy and improve pediatric PBPK models!

Thank you

Questions??