Extrapolation Using PBPK Modeling to Support the Development of Pediatric Products

2026 AGDD Webinar: Bioequivalence Challenges and Approaches of Patient-Centric Oral Formulations

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

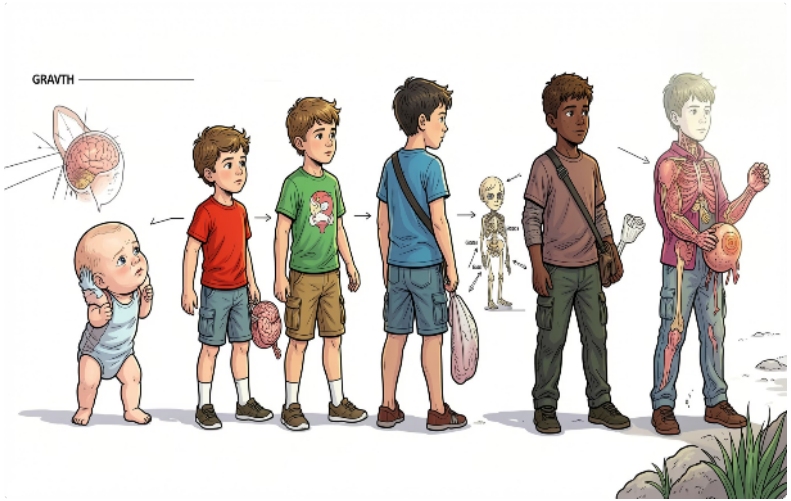
Outline

- Pediatric GI physiology, ontogeny and knowledge gap
- Regulatory guidance for pediatric BA and BE
- PBPK modeling to evaluate BE in pediatrics and carbamazepine case example
- Pediatric formulation complexity
- Path forward and conclusion

GI: Gastrointestinal; PBPK: Physiologically-based pharmacokinetic modeling; BA: Bioavailability; BE, Bioequivalence

Pediatric GI Physiology & Ontogeny

WHAT WE KNOW — AND WHAT WE DON'T



Established Knowledge

- Gastric pH normalizes within days of birth
- GI motility, surface area, and enzyme profiles change with age, affecting dissolution and absorption
- CYP3A4 and transporter ontogeny significantly impacts pre-systemic clearance

Critical Knowledge Gaps

- Bile salt concentrations across pediatric age groups are poorly characterized beyond newborns
- Exogenous factors (e.g., apple juice consumption) can influence transporter activity and drug drug Interaction (DDI) potential

Reference: Burckart GJ et al. "PQRI Workshop: MIDD Approaches in Pediatric Formulation Development." *The AAPS Journal.* 2026

Regulatory Guidance for Pediatric BA/BE

The regulatory framework is evolving, **with PBPK modeling increasingly integrated as a supporting tool**.

ICH E11 (2000)

Recommends relative BA comparisons of pediatric formulations typically be conducted in adults.

ICH E11A (2022)

Provides a roadmap for pediatric extrapolation, guiding how adult data can be applied to pediatric populations.

1 2 3

FDA BE Guidance (2021)

Recommends BE studies in healthy adults, extrapolated to pediatrics.
Applicants should justify extrapolation for children under 6 years.

Reference:
ICH E11 Clinical Investigation of Medicinal Products in the Pediatric Population. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population
ICH E11A Pediatric Extrapolation https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation
Draft Guidance: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application, August 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug

Current Status and FDA's Research Efforts

Current Status of extrapolation for generics:

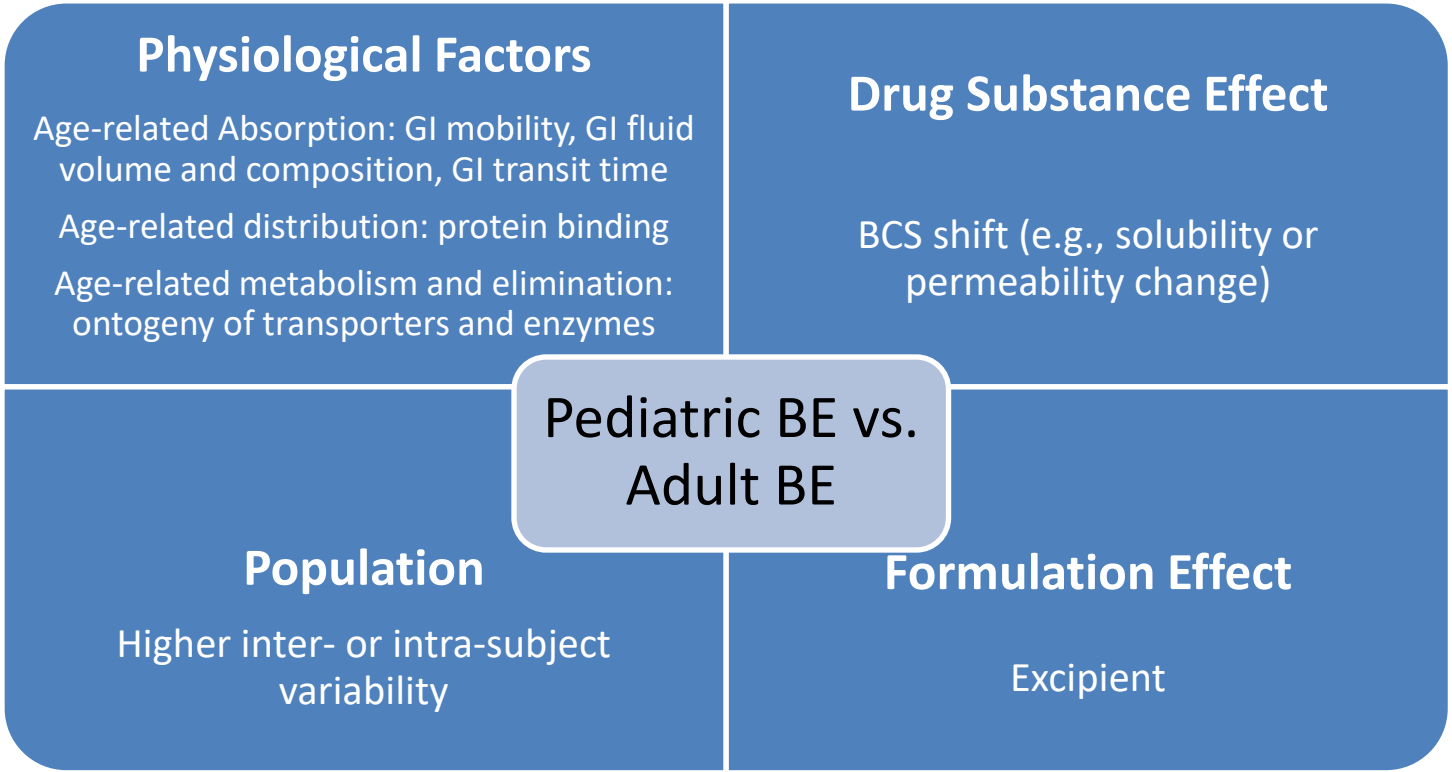
- When waiver options are not available (e.g., oral solutions), generic pediatrics are approved based on adult BE data and we do not believe there is a risk of bio-inequivalence for the approved generic pediatric products.
- We are exploring the evaluation of potential risk via modeling for certain high-risk scenarios.

FDA's research efforts:

Contract Research Project (#HHSF223201810112C): Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

- Comprehensive literature research
- Developing risk mitigation tools based on the totality of evidence
  - Biopharmaceutics Classification System
  - Biorelevant in vitro dissolution testing
  - PBPK modeling

PBPK: Evaluate Interplay between Populations & Formulations



FDA contract: #HHSF223201810112C, Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

BCS: Biopharmaceutics Classification System

PBPK Modeling
A Powerful Tool for Pediatric Drug Development

PBPK modeling integrates **drug-specific properties** (solubility, permeability) with **physiological parameters** (GI motility, fluid volume, transit time) to predict absorption and PK.

Pediatric NDA Submissions

Pediatric PBPK use in NDAs has held steady at **5–15%** (2008–2023), primarily for PK prediction and initial dosing.

Under Age 2

PBPK may be preferred over allometric scaling when ontogeny is a key ADME determinant.

Broader Applications

Predicting DDIs, food effects, and relative BA in pediatrics prior to clinical trials.

Reference: Zhang X et al. Application of PBPK modeling and simulation for regulatory decision making and its impact on US prescribing information: an update on the 2018–2019 submissions to the US FDA's Office of Clinical Pharmacology. *J Clin Pharmacol.* 2020.

Wu F et al. PBPK Modeling to Support BA and BE Assessment in Pediatric Populations. *Pharmaceutical Research.* 2025.

ADME: Absorption, distribution, metabolism and excretion

PBPK to Evaluate Bioequivalence in Pediatrics

- For high-risk scenarios, e.g., narrow therapeutic index (NTI) drugs or drugs with low solubility, using PBPK modeling and simulations as supportive evidence, e.g., by conducting virtual BE assessment in pediatrics

- Case Example : Development of in vitro and in silico methods to provide mechanistic understanding of risks of bioinequivalence for carbamazepine tablets (contract project #HHSF223201810112C with University of Birmingham)

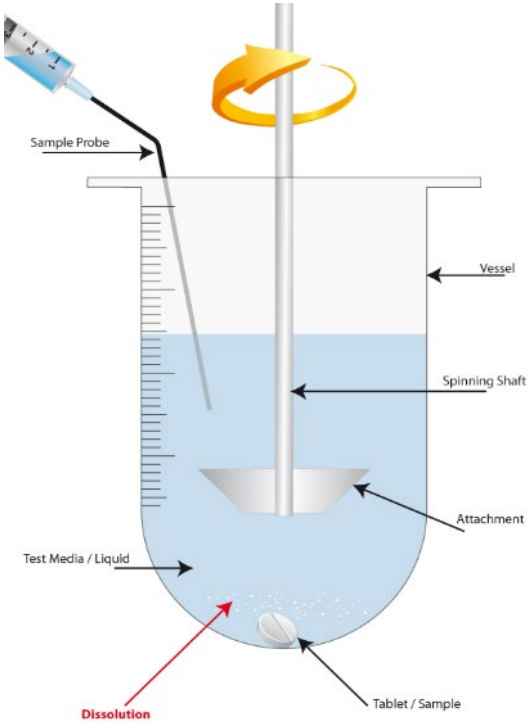
Reference: Pawar G, Wu F, Zhao L, Fang L, Burckart GJ, Feng K, Mousa YM, Al Shoyaib A, Jones MC, Batchelor HK. Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study. AAPS J. 2023;25(4):67.

Note that all subsequent figures and tables related to the carbamazepine case study are taken from or derived from the above reference.

Dissolution Testing for Paediatric Products

There is known variability in GI fluids in children compared to adults

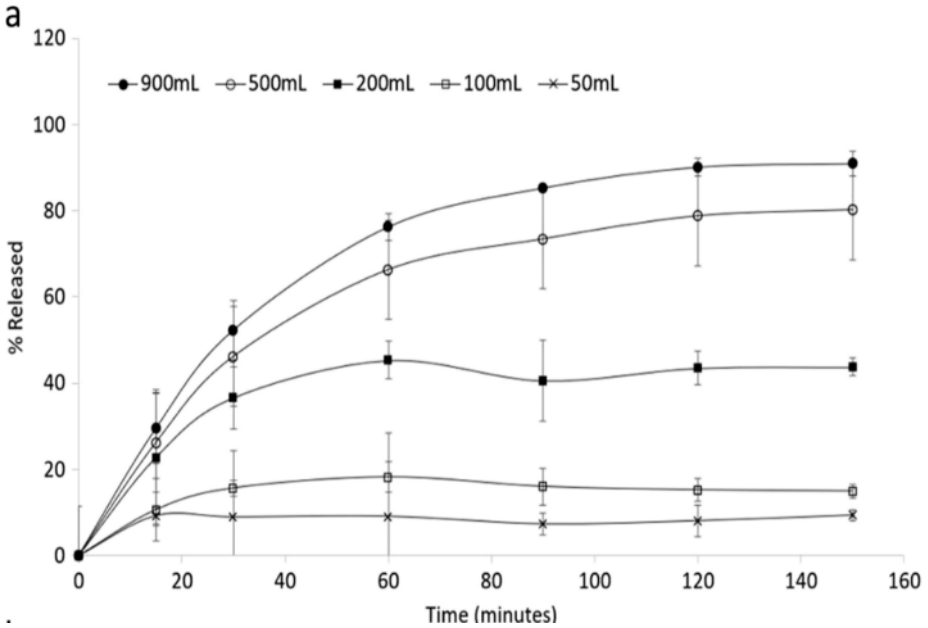
There is a known difference in fluid volume in children compared to adults



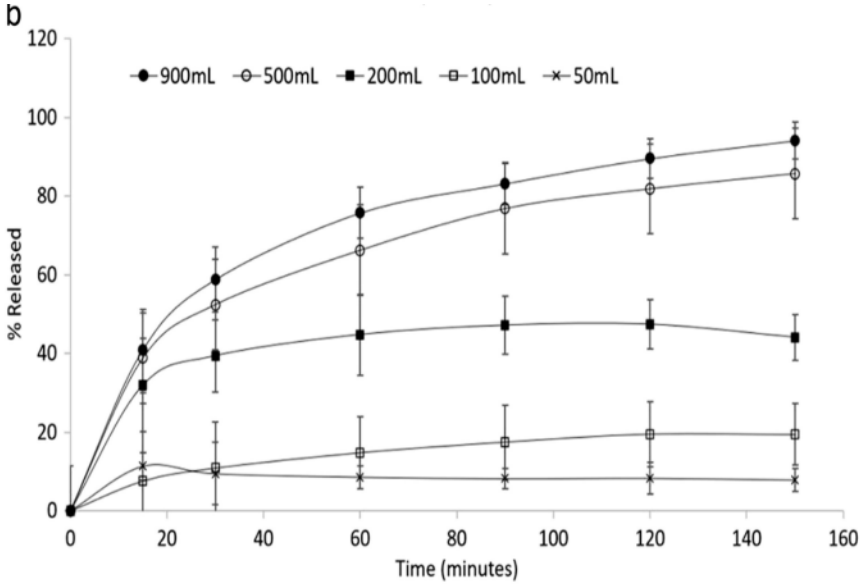
Can we use biorelevant dissolution testing integrated into PBPK modelling for risk assessment/extrapolation for the in vivo performance of paediatric products?

FDA contract: #HHSF223201810112C, Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

Impact of Dissolution Media Volume on Dissolution of 100mg Carbamazepine Tablet



Ad-FaSSGF (a)

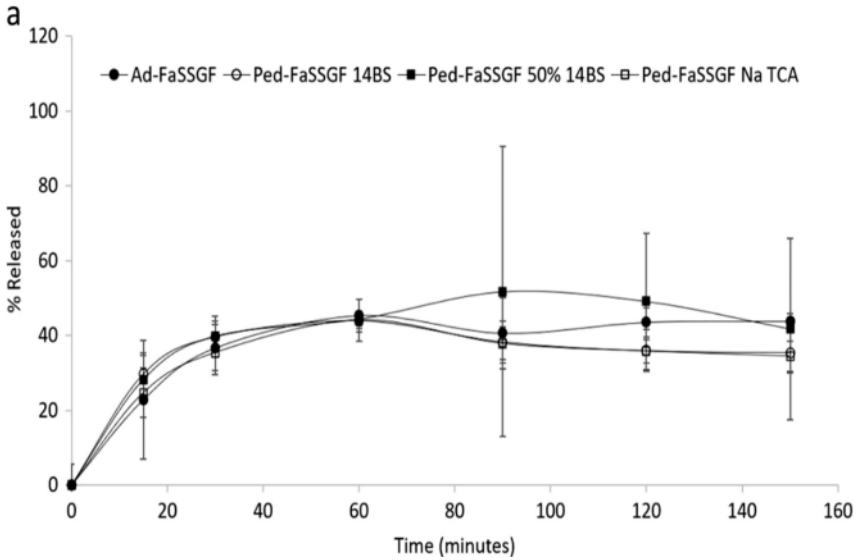


Ad-FaSSIF (b)

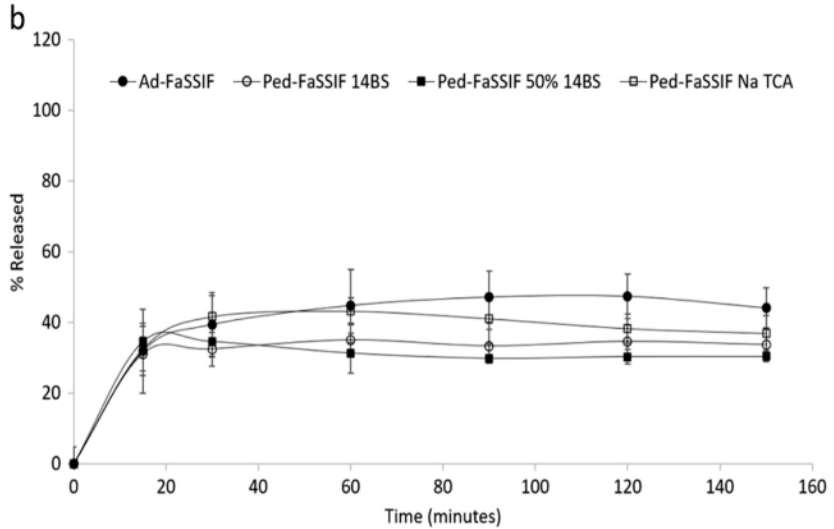
Dissolution profiles of 100 mg CBZ tablets (Tegretol©).
The data points show the mean of 6 values and the error bars show the % CV

FaSSGF: Fasted State Simulated Gastric Fluid; FaSSIF: Fasted State Simulated Intestinal Fluid

Impact of Dissolution Media Composition on Dissolution of 100mg Carbamazepine Tablet in 200mL Media



Simulated gastric fluid (a)

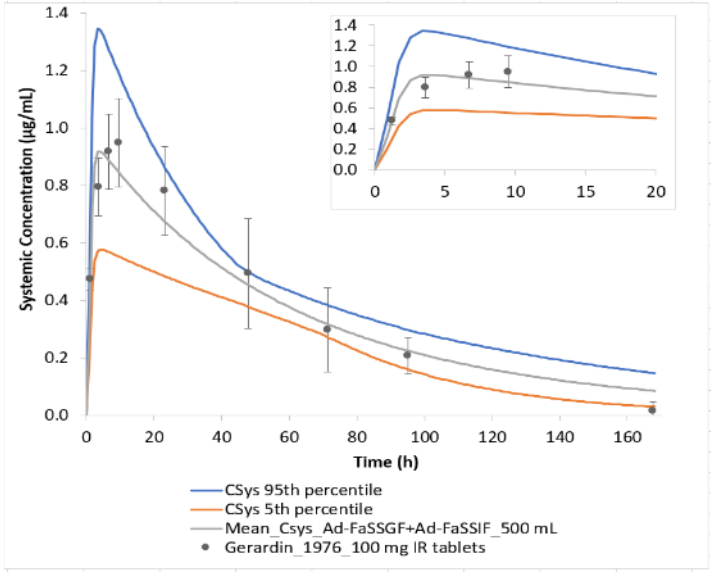


Simulated intestinal fluid (b)

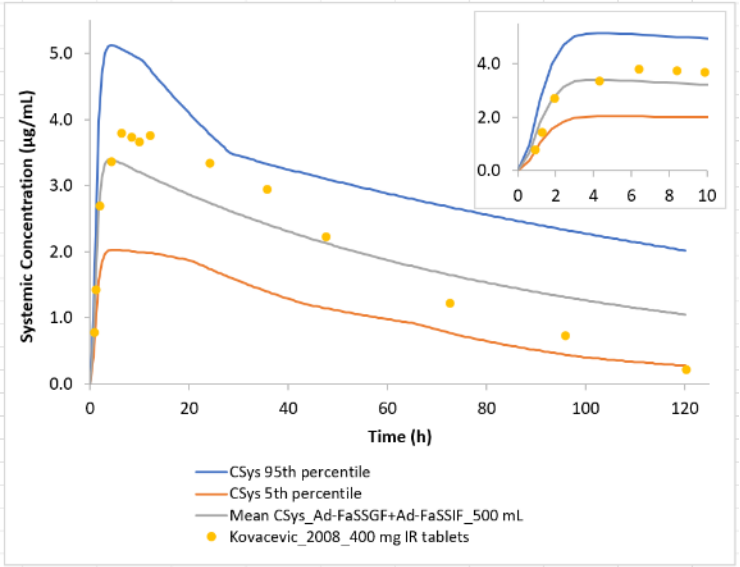
Comparison of the dissolution profiles of 100 mg CBZ tablets (Tegretol©) in 200 mL simulated gastric fluid (**a**) and intestinal fluids (**b**)

Bile salt concentration does not affect dissolution of carbamazepine in simulated media

Adult: Carbamazepine PBPK Model Validation- Using 500mL FaSSGF and FaSSIF Dissolution Data



Clinical data from Gerardin 1976
(n=6 Healthy; oral PK study; 100 mg IR Tegretol).



Clinical data from Kovacevic 2009
(n=18 healthy; 29-37 years; relative BA study; 400 mg (2X 200 mg) IR (Tegretol) tablets SD).

Géradin AP, Abadie FV, Campestrini JA, Theobald W. Pharmacokinetics of carbamazepine in normal humans after single and repeated oral doses. J Pharmacokinet Biopharm. 1976;4(6):521-35.

Kovacević I, Parojcić J, Homsek I, Tubić-Grozdanis M, Langguth P. Justification of biowaiver for carbamazepine, a low soluble high permeable compound, in solid dosage forms based on IVIVC and gastrointestinal simulation. Mol Pharm. 2009;6(1):40-7.

Using Adult Dissolution Data to Predict Exposure in Adults

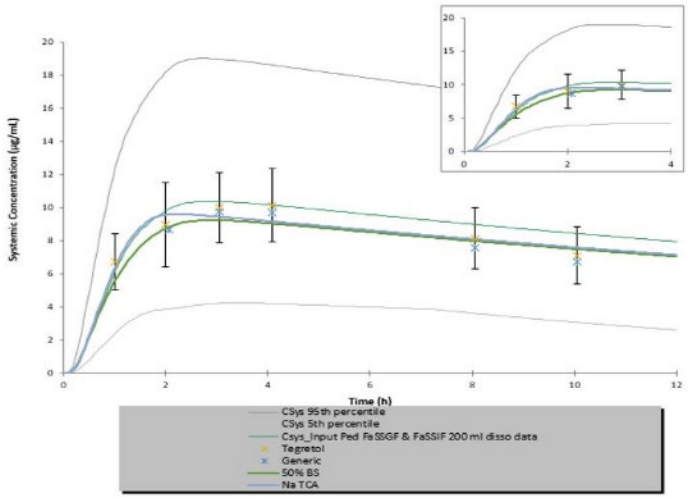
Input dissolution datasets	Clinical study	Details of the study	PK parameter	Mean predicted	Mean observed	PE	FE	AFE	AAFE
Ad-FaSSGF+ FaSSIF 500 mL	Gerardin 1976	100 mg; Tegretol©	AUC_{0-t} (µg/mL.h)	57.0	57.7	-1.2	0.99		
			Cmax (µg/mL)	0.92	0.95	-3.16	0.97	1.21	1.32
		200 mg; Tegretol©	AUC_{0-t} (µg/mL.h)	111	110	0.9	1.01		
			Cmax (µg/mL)	1.64	1.65	-0.61	0.99	1.19	1.31
	Kohlman 2017	200 mg; Tegretol©	AUC_{0-t} (µg/mL.h)	121	127	-4.6	0.95		
			Cmax (µg/mL)	2.22	2.0	11.0	1.11	1.12	1.15
		400 mg; Tegretol©	AUC_{0-t} (µg/mL.h)	209.75	207	1.3	1.01		
			Cmax (µg/mL)	4.51	4.0	12.8	1.13	1.35	1.37
	Kovacevic 2009	Single 400 mg Tegretol© (2X200 mg)	AUC_{0-t} (µg/mL.h)	237	225	5.3	1.05		
			Cmax (µg/mL)	3.39	3.79	-10.6	0.89	1.13	1.39
	Olling 1999	Single 400 mg Tegretol© (2X200 mg)	AUC_{0-t} (µg/mL.h)	252	281	-10.5	0.90		
			Cmax (µg/mL)	4.73	4.24	11.6	1.12	0.97	1.20

The input dissolution (500mL Ad FaSSGF/FaSSIF) provides a good prediction to the clinical data

Target is PE<20%

Kohlmann P, Stillhart C, Kuentz M, Parrott N. Investigating Oral Absorption of Carbamazepine in Pediatric Populations. The AAPS Journal. 2017;19(6):1864-77. Olling M, Mensinga TT, Barends DM, Groen C, Lake OA, Meulenbelt J. Bioavailability of carbamazepine from four different products and the occurrence of side effects. Biopharm Drug Dispos. 1999;20(1):19-28

Pediatric: Carbamazepine PBPK Model Validation Using 200mL Pediatric Dissolution Media



Clinical data from Hartley 1991
(n=12 children aged 6.5-15 years taking CBZ as either 100 or 200mg tablets twice daily).

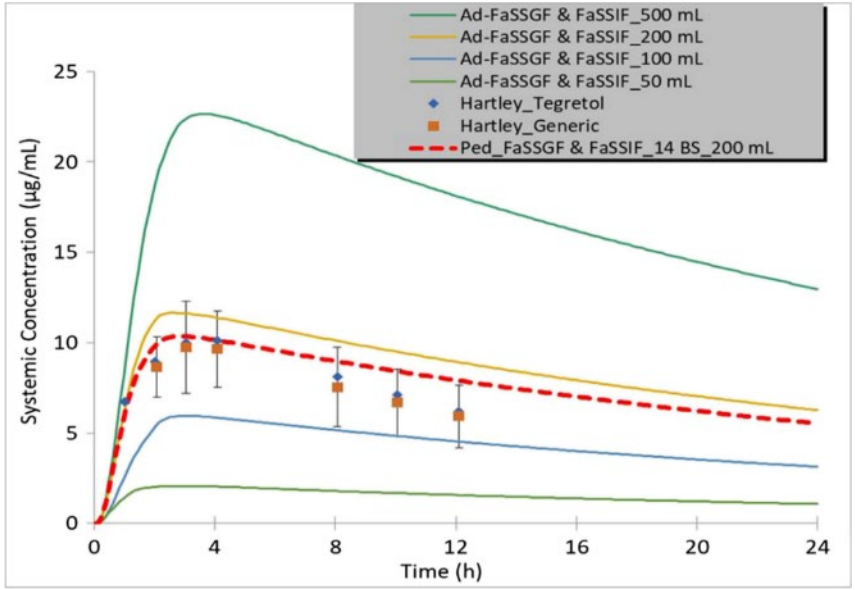
Input dissolution datasets	PK parameter	Mean predicted	Mean observed	PE
Ped-FaSSGF + FaSSIF 14 BS 200 mL	AUC_{0-t} (µg/mL.h)	103	99	4.04
	Cmax (µg/mL)	10.4	10.1	2.97
Ped-FaSSGF + FaSSIF 50% 14 BS 200 mL	AUC_{0-t} (µg/mL.h)	92	99	− 7.07
	Cmax (µg/mL)	9.23	10.1	− 8.61
Ped-FaSSGF + FaSSIF Na TCA 200 mL	AUC_{0-t} (µg/mL.h)	94.7	99	− 4.34
	Cmax (µg/mL)	9.59	10.1	− 5.05

Dissolution data from 200mL pediatric media provided good prediction of to clinical data.

Target is PE<20%

Hartley R, Aleksandrowicz J, Bowmer CJ, Cawood A, Forsythe WI. Dissolution and relative bioavailability of two carbamazepine preparations for children with epilepsy. Journal of Pharmacy and Pharmacology. 1991;43(2):117-9.

Using Biorelevant Dissolution Data to Predict Exposure in Pediatric Populations



Input dissolution datasets	Clinical study reported in	PK parameter	Mean predicted[a]	Mean observed[b]	PE
Ped-FaSSGF + FaSSIF 14 BS 200 mL	Hartley (1991)	AUC_{0-t} (µg/mL.h)	103	99	4.04
		Cmax (µg/mL)	10.4	10.1	2.97
Ped-FaSSGF + FaSSIF 50% 14 BS 200 mL	Hartley (1991)	AUC_{0-t} (µg/mL.h)	92	99	-7.07
		Cmax (µg/mL)	9.23	10.1	-8.61
Ped-FaSSGF + FaSSIF Na TCA 200 mL	Hartley (1991)	AUC_{0-t} (µg/mL.h)	94.7	99	-4.34
		Cmax (µg/mL)	9.59	10.1	-5.05
Ad-FaSSGF + FaSSIF 500 mL	Hartley (1991)	AUC_{0-t} (µg/mL.h)	224	99	126
		Cmax (µg/mL)	23.0	10.1	128
Ad-FaSSGF + FaSSIF 200 mL	Hartley (1991)	AUC_{0-t} (µg/mL.h)	116	99	17.2
		Cmax (µg/mL)	12.0	10.1	18.8
Ad-FaSSGF + FaSSIF 100 mL	Hartley (1991)	AUC_{0-t} (µg/mL.h)	58.2	99	-41.2
		Cmax (µg/mL)	6.0	10.1	-40.6
Ad-FaSSGF + FaSSIF 50 mL	Hartley (1991)	AUC_{0-t} (µg/mL.h)	21.0	99	-78.8
		Cmax (µg/mL)	2.10	10.1	-79.2

Dissolution data from 200mL Ped FaSSGF/FaSSIF 14 BS media was closest to the clinical data although a slightly lower volume may have provided a more accurate prediction

Clinical data from Hartley 1991
(n=12 children aged 6.5-15 years taking CBZ as either 100 or 200mg tablets twice daily).

Target is PE<20%

Hartley R, Aleksandrowicz J, Bowmer CJ, Cawood A, Forsythe WI. Dissolution and relative bioavailability of two carbamazepine preparations for children with epilepsy. Journal of Pharmacy and Pharmacology. 1991;43(2):117-9.

Virtual Bioequivalence Studies: Population 100 mg Dose-Tegretol and Generic CBZ

Population (100 mg dose-Tegretol© and generic CBZ; simulation run time-24 h)	Cross-over design	Input dissolution datasets	VBE outcome: 90% CIs (GMR)- (lower limit-upper limit)		Bioequivalence Yes, or No?
			AUC (µg/mL h)	Cmax (µg/mL)	
Adult	N = 10 trials; n = 12 subjects	Only Ad-FaSSIF 500 mL	94.8 (94.6–95.0)	94.5 (94.3–94.7)	Yes
	N = 10 trials, n = 12 subjects	Ad-FaSSGF and FaSSIF 500 mL	105 (105–106)	105 (104–105)	Yes
	N = 10 trials; n = 16 subjects	Ad-FaSSGF and FaSSIF 500 mL	105 (105–106)	105 (105–105)	Yes
	N = 10 trials; n = 24 subjects	Ad-FaSSGF and FaSSIF 500 mL	105 (105–105)	105 (104–105)	Yes
	N = 10 trials; n = 48 subjects	Only adult FaSSIF 500 mL	94.8 (94.7–94.9)	94.5 (94.4–94.6)	Yes
	N = 10 trials; n = 48 subjects	Ad-FaSSGF and FaSSIF 500 mL	106 (105–106)	105 (105–105)	Yes
Pediatrics	N = 10 trials; n = 12 subjects	Only Ped-FaSSIF 200 mL_14 BS	98.9 (98.2–99.7)	101 (101–102)	Yes
	N = 10 trials; n = 12 subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	112 (111–114)	113 (112–114)	Yes
	N = 10 trials; n = 16 subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	113 (112–114)	113 (112–114)	Yes
	N = 10 trials; n = 24 subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	112 (111–113)	113 (112–113)	Yes
	N = 10 trials; n = 48 subjects	Only Ped- FaSSIF 200 mL_14 BS	98.9 (98.5–99.3)	101 (101–102)	Yes
	N = 10 trials; n = 48 subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	112 (111–113)	112 (112–113)	Yes

Summary: Carbamazepine Case Study

- Carbamazepine dissolution is more sensitive to volume compared to bile salt concentration
- Dissolution input for adults of 500mL Adult FaSSGF and FaSSIF media gave a good match to the existing clinical data
- Dissolution input for pediatric populations using 200 mL Pediatric FaSSGF and FaSSIF media gave a good match to the existing clinical data
- Using adult dissolution media to predict exposure in pediatric populations was strongly influenced by volume with 200mL providing the closest match. However, a volume of ~150-200 may be superior.
- The VBE showed equivalence based on dissolution inputs. As the dissolution profiles were similar, this is unsurprising.

In Vitro Dissolution Testing for Pediatric Products

Medium Volume Over Composition

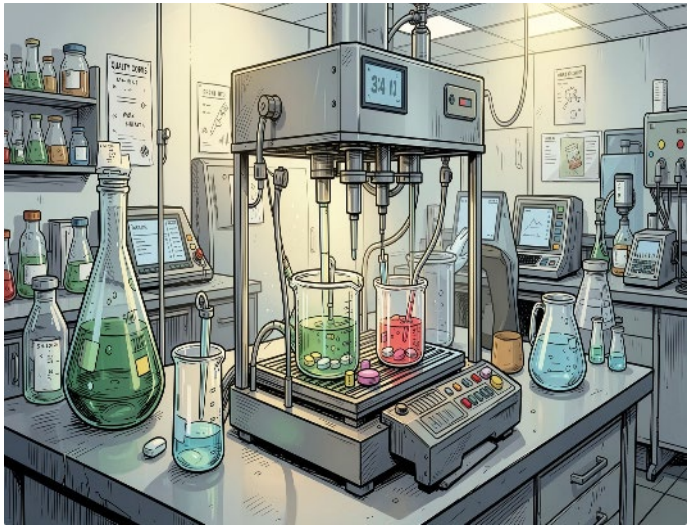
Dissolution medium volume is more critical than composition for mimicking pediatric GI conditions. Adjusting from 500 mL (adult) to 200 mL was a key factor in the carbamazepine case study.

Biorelevant Data Integration

Biorelevant dissolution data incorporated into PBPK models can support relative BA and BE assessment — providing a mechanistic link between in vitro performance and predicted in vivo outcomes.

Food and Dosing Vehicle Variability

The type of food (yogurt vs. applesauce vs. juice) and its composition varies by region, contributing to observed population PK variability — a factor requiring careful consideration in model design.



Reference: Wu F et al. “PBPK Modeling to Support BA and BE Assessment in Pediatric Populations”. *Pharmaceutical Research.* 2025.

Pediatric Formulation Complexity

Taste Masking & Excipients

Pediatric formulations often require taste-masking excipients or crushing — each modification can alter absorption. Excipients may differentially affect GI motility and transporter activity in children vs. adults.

Enteric Coating Challenges

Food co-administration may alter pH-triggered release profiles in pediatrics. Mechanistic PBPK modeling offers advantages over empirical approaches for predicting these complex scenarios.

Drug-Food Binding

Binding of drugs to infant formula or dairy is an important stability and absorption consideration. Mechanistic PBPK may incorporate this, though further model development and validation are needed.

Reference: Wu F et al. “PBPK Modeling to Support BA and BE Assessment in Pediatric Populations”. *Pharmaceutical Research.* 2025.

Path Forward

PBPK is a Validated Tool

Supports relative BA and BE assessment for pediatric populations where clinical studies are conducted in adults or healthy subjects.

Totality of Evidence

All available data — drug substance, formulation, dissolution, and pediatric physiology — need to be integrated into a mechanistic PBPK model for sound regulatory decisions.

Model Quality is Critical

Right assumptions, right data, right structure, and right ADME expectations are all essential. Validation is a prerequisite, not an afterthought.

Collaboration in the Future

Continued partnership between regulatory agency, industry, and academia is essential to bridge data gaps and advance the field of pediatric drug development.

Reference: Wu F et al. “PBPK Modeling to Support BA and BE Assessment in Pediatric Populations”. *Pharmaceutical Research.* 2025.

Conclusion

- For high-risk scenarios, e.g., NTI drugs or drugs with low solubility, PBPK modeling and simulations may be used as supportive evidence (e.g., conducting virtual BE assessment in pediatrics).
- With continuous improvement to the models along with additional research and applied regulatory experiences, PBPK absorption modeling and simulations would aid in mitigating the risk of bioinequivalence or undesired relative bioavailability to ensure development of safe and effective pediatric generic drug products.
- The Agency encourages applicants to submit modeling and simulation data and communicate at an early stage, e.g., via pre-ANDA meeting or controlled correspondence or model integrated evidence (MIE) pilot program.

Recent Relevant Publications Supported by Our Internal and External Research

Pharmaceutical Research (2025) 42:847–855
https://doi.org/10.1007/s11095-025-03846-y

FDA MODELING MASTER FILE

PBPK Modeling to Support Bioavailability and Bioequivalence Assessment in Pediatric Populations

Fang Wu[1] · Eleftheria Tsakalozou[1] · Gilbert J. Burckart[2] · Rebeka Žakelj[3] · Lu Gaohua[4] · Kazuko Sagawa[5] · Viera Lukacova[6] · Siva Vaithiyalingam[7] · Jianghong Fan[2] · Nikoletta Fotaki[8] · Nikunjkumar Patel[9] · Lanyan Fang[1]

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The AAPS Journal (2026) 28:68
https://doi.org/10.1208/s12248-026-01217-y

MEETING REPORT

PQRI Workshop: Model-Informed Drug Development (MIDD) Approaches in Pediatric Formulation Development

Gilbert J. Burckart[1] · Susan Abdel-Rahman[1] · Caleb Choi[1] · M. Petrea Cober[2] · James E. Cummins Jr.[3] · Nikoletta Fotaki[4] · Daniel Gonzalez[5] · David Harris[6] · Neil Parrott[7] · Hardikkumar Patel[8] · Fang Wu[9] · Andreas Abend[6]

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The AAPS Journal (2020) 22: 107
DOI: 10.1208/s12248-020-00493-6

Research Article

Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations

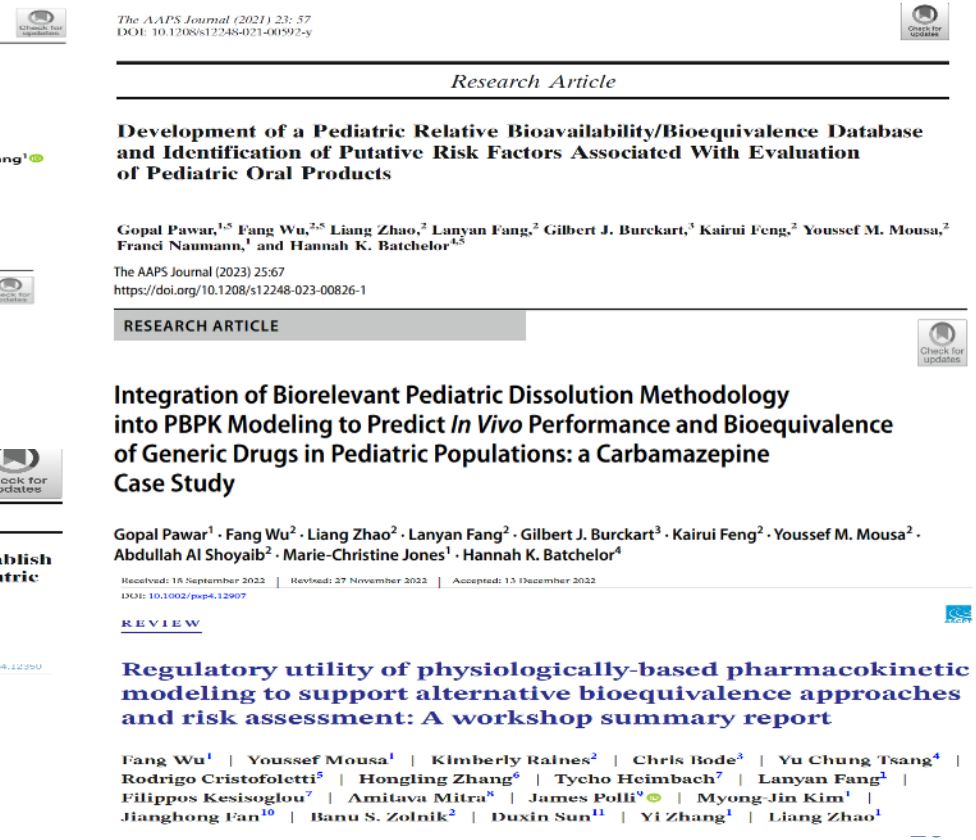
Lei Miao,[1] Youssef M. Mousa,[1] Liang Zhao,[1] Kimberly Raines,[2] Paul Seo,[2] and Fang Wu[1,3]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 158–166; doi:10.1002/psp4.12350

ARTICLE

Assessing CYP2C19 Ontogeny in Neonates and Infants Using Physiologically Based Pharmacokinetic Models: Impact of Enzyme Maturation Versus Inhibition

Peng Duan[1], Fang Wu[1], Jason N. Moore[2], Jeffrey Fisher[3], Victor Crentsil[4], Daniel Gonzalez[5], Lei Zhang[6], Gilbert J. Burckart[2] and Jian Wang[7]*



The AAPS Journal (2021) 23: 57
DOI: 10.1208/s12248-021-00592-y

Research Article

Development of a Pediatric Relative Bioavailability/Bioequivalence Database and Identification of Putative Risk Factors Associated With Evaluation of Pediatric Oral Products

Gopal Pawar,[1,5] Fang Wu,[2,5] Liang Zhao,[2] Lanyan Fang,[2] Gilbert J. Burckart,[3] Kairui Feng,[2] Youssef M. Mousa,[2] Franci Naumann,[1] and Hannah K. Batchelor[4,5]

The AAPS Journal (2023) 25:67
https://doi.org/10.1208/s12248-023-00826-1

RESEARCH ARTICLE

Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict *In Vivo* Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study

Gopal Pawar[1] · Fang Wu[2] · Liang Zhao[2] · Lanyan Fang[2] · Gilbert J. Burckart[3] · Kairui Feng[2] · Youssef M. Mousa[2] · Abdullah Al Shoyaib[2] · Marie-Christine Jones[1] · Hannah K. Batchelor[4]

Received: 18 September 2022 | Revised: 27 November 2022 | Accepted: 13 December 2022
DOI: 10.1002/psp4.12907

REVIEW

Regulatory utility of physiologically-based pharmacokinetic modeling to support alternative bioequivalence approaches and risk assessment: A workshop summary report

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