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Physiologically Based Pharmacokinetic Absorption Modeling for Bioequivalence Evaluation in Adult and Pediatric Populations

2024 PQRI Workshop: MIDD Approaches in Pediatric Formulation Development

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Disclaimer

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Outline

- Risk factors associated with significant differences in PK parameters in pediatrics
- PBPK modeling and simulations for bioequivalence evaluation in adult and pediatric populations:

  Carbamazepine and Oseltamivir case examples
- Challenges and opportunities for developing and applying PBPK absorption models for pediatrics

FDA's Research Efforts

Contract Research Project: 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
  - Biopharmaceutics Classification System
  - Biorelevant in vitro dissolution testing
  - PBPK modeling

Putative Risk Factors: RLD vs. Test in Pediatrics

	Putative risk factors	Number of studies identified
Physiological factors (ADME effect)	Age-related absorption effects (e.g., GI motility, GI fluid volume or composition, and GI transit time)	28
	Age-related distribution effects (e.g., protein binding)	2
	Age-related metabolism or clearance effects	15
Drug substance or formulation effects	Drug substance effect (e.g., alternative salt or polymorphic form of drug substance)	5
	Drug product/formulation effects	12
Disease	Age-related disease progression and other disease-related effects	4
Population characteristics	High inter- and/or intra-individual variabilities	18
Study design	Non-equivalent dose effects	2
	Accuracy of administered dose	2
	Poor study design including small sample size	11

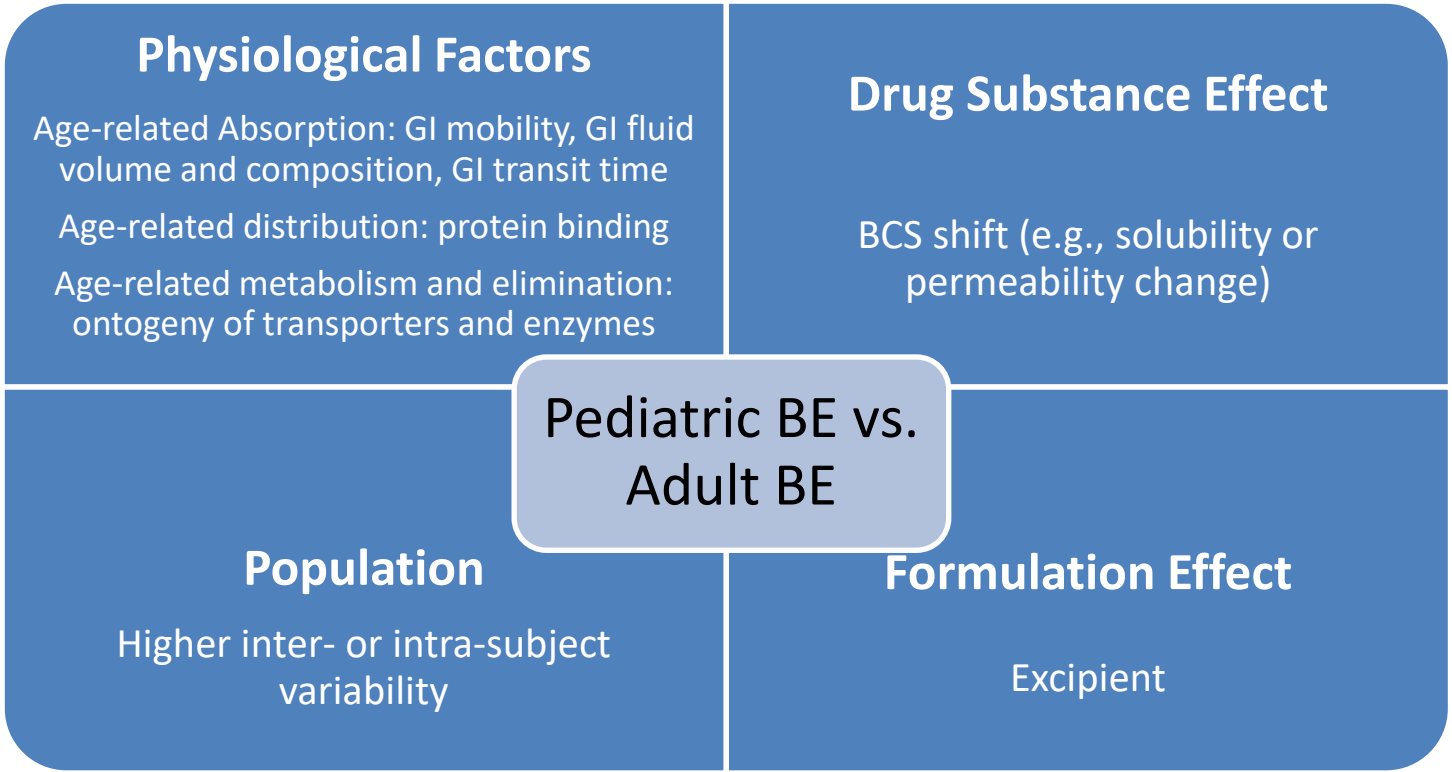
- *Note that multiple risk factors may have been extracted from one study*
- Risks were found being associated with products with API belonging to NTI drug category, The drug solubility is low (BCS class II or IV)

Research results from FDA contract: ORS-EXT-2018-09, Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

Pawar G, Wu F, Zhao L, Fang L, Burckart GJ, Feng K, Mousa YM, Naumann F, Batchelor HK. AAPS J. 2021 Apr 21;23(3):57. doi: 10.1208/s12248-021-00592-y. AAPS Journal, 2021

RLD: reference listed drug

PBPK: Evaluate Interplay between Populations & Formulations



FDA contract: ORS-EXT-2018-09, Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

BE: Bioequivalence; BCS: Biopharmaceutics Classification System

PBPK Modeling to Evaluate High Risk Scenarios

- 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 1: Development of in vitro and in silico methods to provide mechanistic understanding of risks of bioinequivalence for carbamazepine tablets (contract project with University of Birmingham, BAA #HHSF223201810112C for Research for NTI and BCS class II model drugs)

- Case Example 2: Application of PBPK modeling to determine bioequivalent dissolution "Safe Space" for Oseltamivir Phosphate (OP) (Note that this example is for demonstrating a PBPK tool and OP is a putative BCS Class I/III drug)

Reference:

- 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 Journal. 2023;25(4):67.
- Using a physiologically-based pharmacokinetic absorption model to establish dissolution bioequivalence safe space for oseltamivir in adult and pediatric populations. AAPS Journal, 2020; 22(5):107

Case Example 1: PBPK for Carbamazepine Tablets

Purpose:

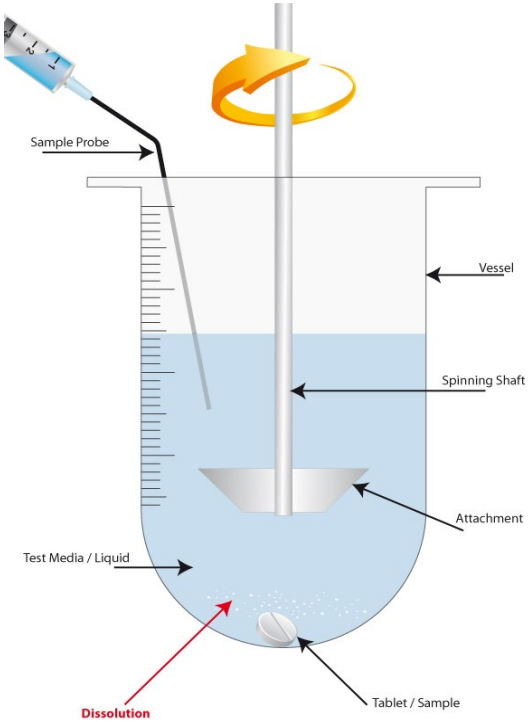
- Development of in vitro and in silico methods to provide mechanistic understanding of risks of bioinequivalence for carbamazepine tablets

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.

Dissolution and Risks of non-BE

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

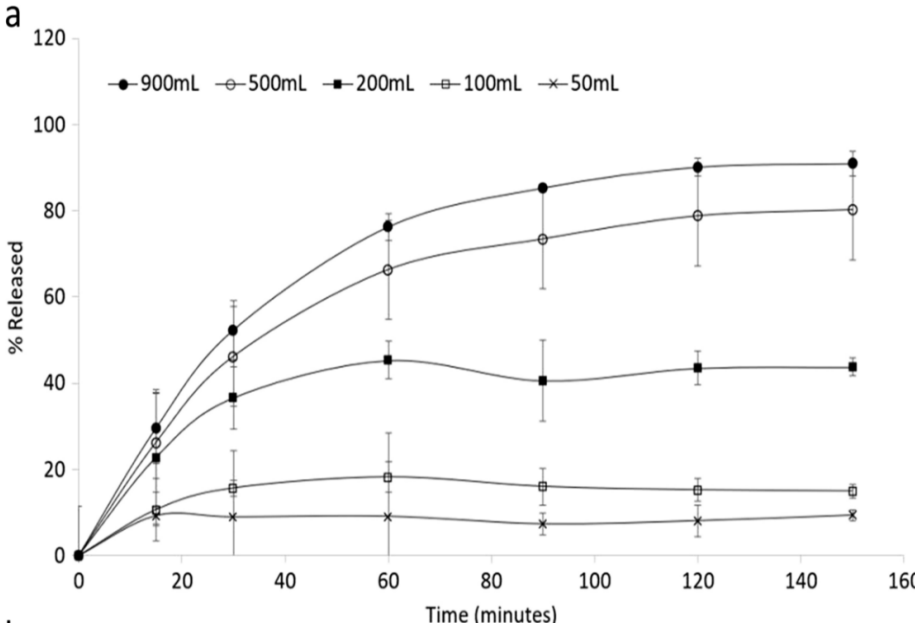
There is a known difference in fluid volume in children compared to adults



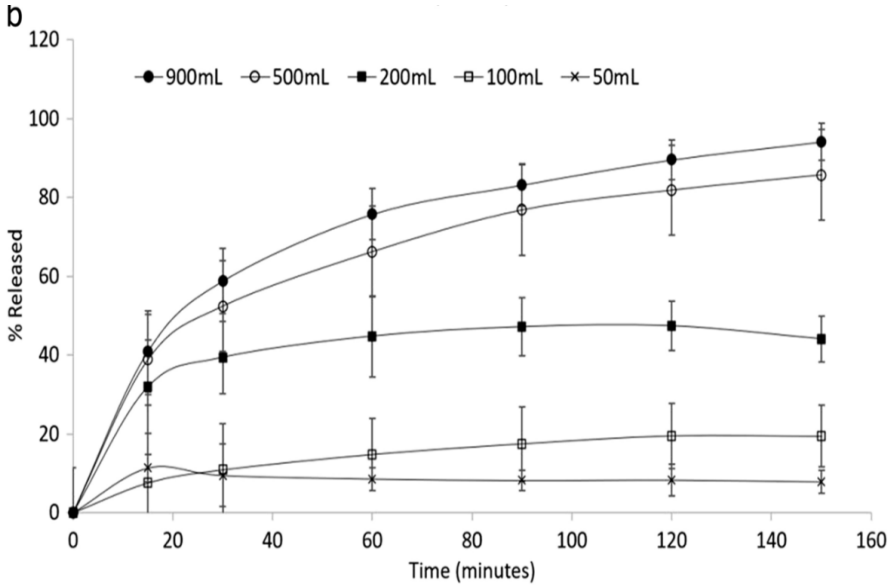
Can we use biorelevant dissolution testing integrated into PBPK modelling to predict a risk of bioinequvialence in pediatrics?

FDA contract: ORS-EXT-2018-09, 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)

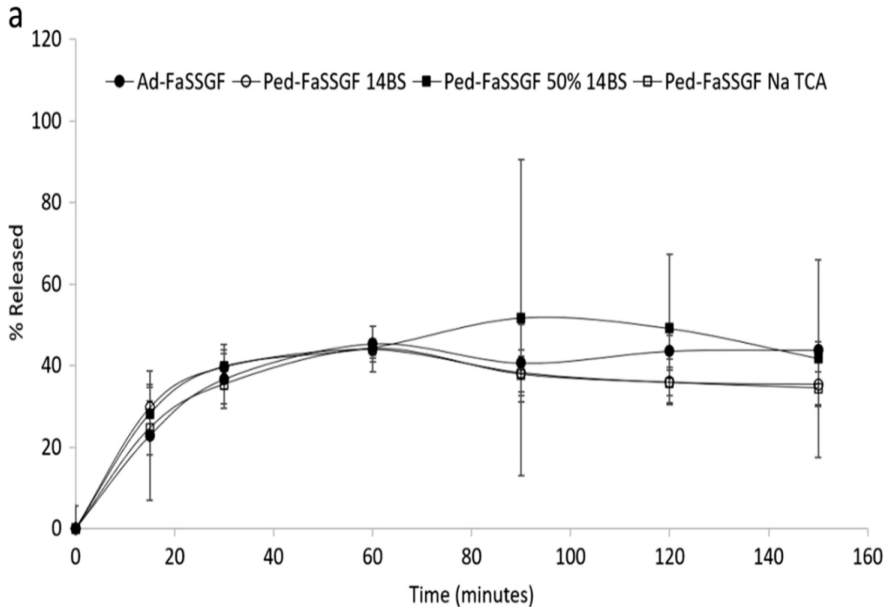


Ad-FaSSIF (b)

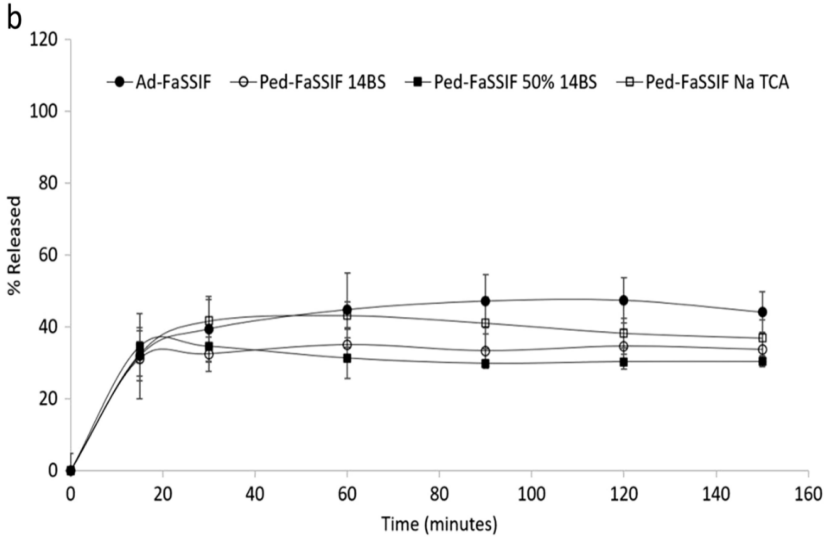
Dissolution profiles of 100 mg CBZ tablets (Tegretol©).
The data points show the mean of 6 values and the error bars show the % CV

As expected, media volume affects dissolution for carbamazepine as a poorly soluble drug

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



Simulated gastric fluid (a)

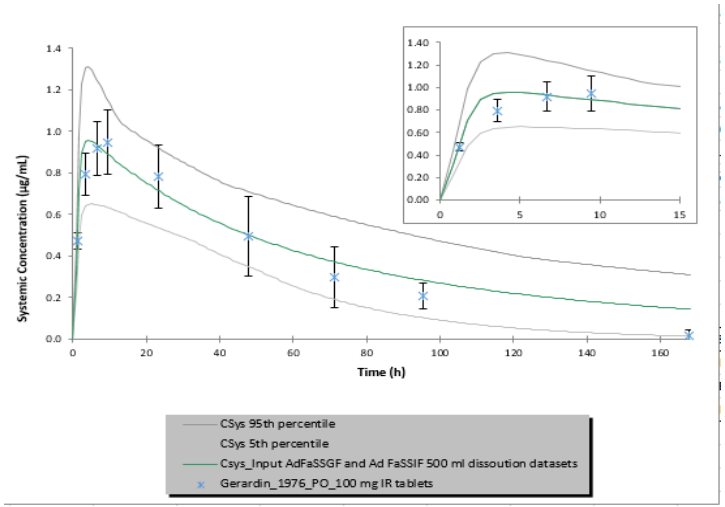


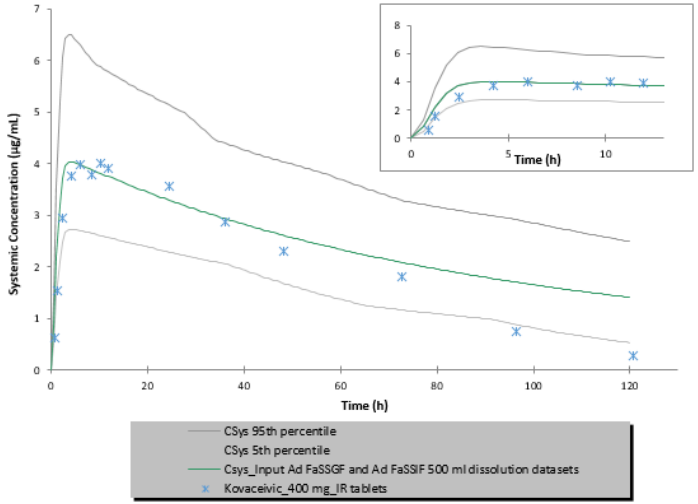
Simulated intestinal fluid (b)

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).

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. doi: 10.1007/bf01064556.

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

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. doi: 10.1021/mp800128y.

Using Adult Dissolution Data to Predict Exposure in Adults

Clinical study	Details of the study	PK parameter	Mean Predicted	Mean observed	PE
Gerardin 1976	PK study; Healthy fasting volunteers n=6; Single oral dose 100 mg;	AUC_{0-t} (µg/mL.h)	66.16	58	14.06
		Cmax (µg/mL)	0.96	0.95	1.07
Gerardin 1976	PK study; Healthy fasting volunteers n=6; Single oral dose 200 mg;	AUC_{0-t} (µg/mL.h)	126.7	113	12.13
		Cmax (µg/mL)	1.71	1.65	3.57
Kohlman 2017	Meta-analysis (mean-weighted profiles); n=76; 200 mg	AUC_{0-t} (µg/mL.h)	122.26	121	1.04
		Cmax (µg/mL)	2.16	1.99	8.54
Kohlman 2017	Meta-analysis (mean-weighted profiles); n=94; 400 mg	AUC_{0-t} (µg/mL.h)	206.277	207	-0.35
		Cmax (µg/mL)	4.322	4.01	7.78
Kovacevic 2009	Relative bioavailability; Healthy fasting volunteers (n=18; 29-37 years); 400 mg (2 IR tablets);	AUC_{0-t} (µg/mL.h)	294.5	224	31.47
		Cmax (µg/mL)	4.036	3.78	6.79
Olling 1999	Relative bioavailability; Healthy fasting volunteers (n=18; 20-38 years); 200 mg; 150 mL water;	AUC_{0-t} (mg/L.h)	318.88	317.0	0.59
		Cmax (mg/L)	5.63	5.0	12.69

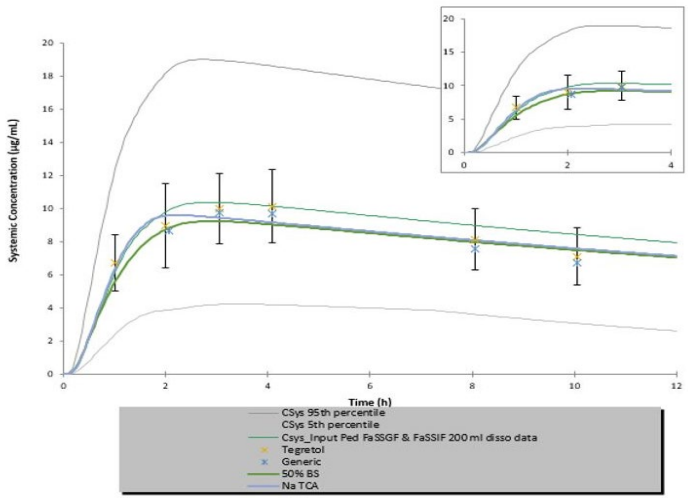
The input dissolution (500mL Ad FaSSGF/FaSSIF) provides a good prediction to the clinical data

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. doi: 10.1208/s12248-017-0149-6

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. doi: 10.1002/

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



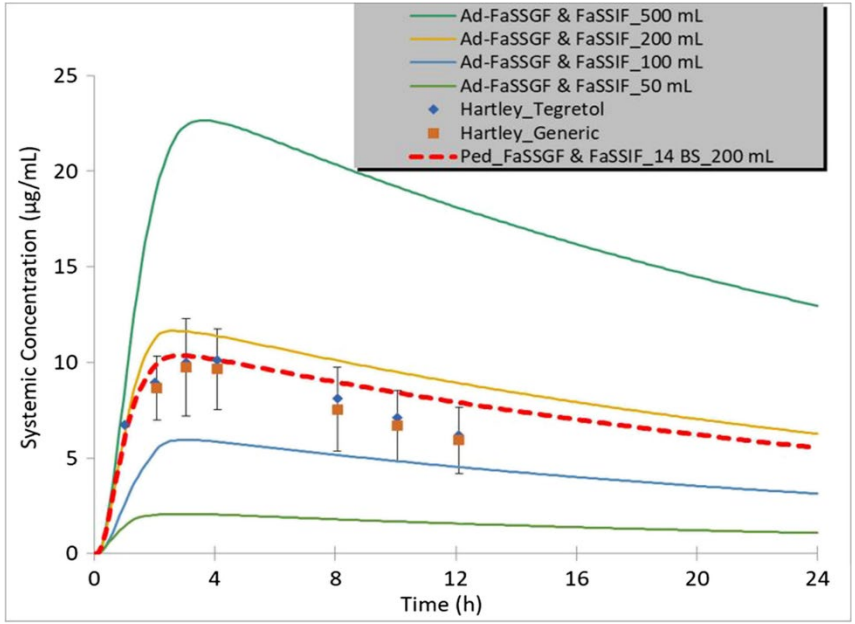
Clinical data from Hartley 1991
(n=12 children aged 6.5-15 years taking CBZ as either 100 or 200mg tablets twice daily).

Input dissolution datasets	PK parameter	Mean Predicted	Mean observed	PE
Ped-FaSSGF/FaSSIF 14 BS 200 mL	AUC_{0-t} (µg/mL.h)	103.24	99	4.29
	Cmax (µg/mL)	10.35	8.2	26.3
Ped-FaSSGF/FaSSIF 50% 14 BS 200 mL	AUC_{0-t} (µg/mL.h)	92.0	99	-7.07
	Cmax (µg/mL)	9.23	8.2	12.5
Ped-FaSSGF/FaSSIF Na TCA 200 mL	AUC_{0-t} (µg/mL.h)	94.70	99	-4.34
	Cmax (µg/mL)	9.588	8.2	16.92

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. doi: https://doi.org/10.1111/j.2042-7158.1991.tb06644.x.

Using Biorelevant Dissolution Data to Predict Exposure in Pediatric Populations



Input dissolution datasets	PK parameter	Mean Predicted	Mean observed	PE
Ad-FaSSGF/FaSSIF 500 mL	AUC (µg/mL.h)	224	99	126.3
	Cmax (µg/mL)	23	8.2	180.5
Ad-FaSSGF/FaSSIF 200 mL	AUC (µg/mL.h)	116	99	17.2
	Cmax (µg/mL)	12	8.2	46.3
Ad-FaSSGF/FaSSIF 100 mL	AUC (µg/mL.h)	58.2	99	-41.2
	Cmax (µg/mL)	6.0	8.2	-26.8
Ad-FaSSGF/FaSSIF 50 mL	AUC (µg/mL.h)	21	99	-78.8
	Cmax (µg/mL)	2.1	8.2	-74.4
Ped-FaSSGF/FaSSIF NaTCA 200 mL	AUC (µg/mL.h)	103.25	99	-4.34
	Cmax (µg/mL)	10.35	8.2	16.92

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. doi: https://doi.org/10.1111/j.2042-7158.1991.tb06644.x.

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

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.

Summary: Carbamazepine Case Study

- Carbamazepine dissolution is more sensitive to volume compared to bile salt concentration
- Dissolution input for adults of 500mL Ad FaSSGF or Ad FaSSIF media gave a good match to the existing clinical data
- Dissolution input for pediatric populations using 200 mL Ped 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 approximation. 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.

Case Example 2: PBPK for Oseltamivir

Purpose:

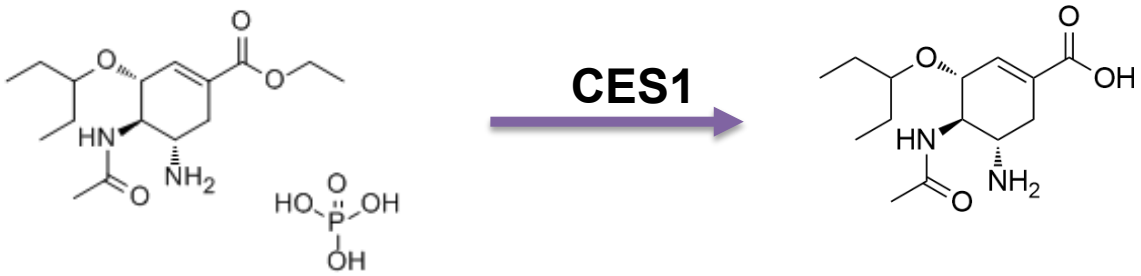
- Develop a PBPK model for a putative BCS Class I/III drug, oseltamivir phosphate (OP) and its metabolite oseltamivir carboxylate (OC) in both adults and pediatrics
- Conduct virtual BE simulations to establish BE dissolution safe space for OP in both adults and pediatrics

Reference: Miao L, Mousa Y, Zhao L , Raines K, Seo P, Wu F. Using a physiologically-based pharmacokinetic absorption model to establish dissolution bioequivalence safe space for oseltamivir in adult and pediatric populations. AAPS Journal, 2020. DOI : 10.1208/s12248-020-00493-6

Background

Oseltamivir Phosphate (OP)

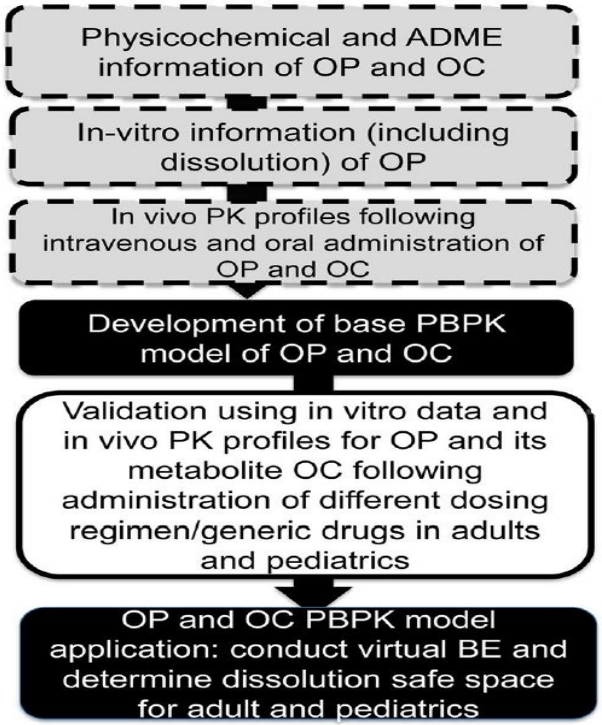
- Antiviral medication, for influenza A and B
- A pro-drug of the active metabolite Oseltamivir Carboxylate (OC)



OP **OC**

PBPK Model Development

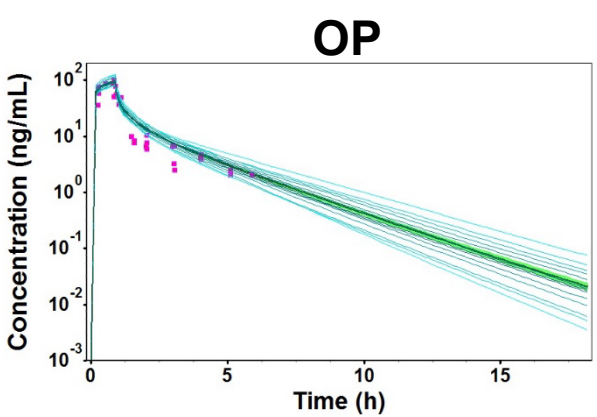
Properties	Value
LogP (OP/OC)	0.36/− 2.1
Molecular weight (OP/OC)	312/284
pKa (OP/OC)	7.70/8.2
Distribution	
Human blood to plasma ratio (OP/OC)	1/0.6
Fraction unbound in plasma (OP/OC)	58%/97%
Elimination	
CL_{renal} (L/h) (OP/OC)	4.2/18.8 (adults, for i.v. and oral)
V_{max} (mg/s/mg-CES1)*	0.52 (adults, for i.v. and oral) 0.53 (9–18 years, 1–5 years, 3–9 months, 0–2 months)
K_m (mg/L)*	599 (adults, for i.v. and oral) 431.4 (3–9 months, 1–5 years, and 9–18 years) 331.1 (0–2 months)
CES1 (mg/g tissue)	0.12 (adult) 0.04 (0–2 months) 0.06 (3–6 months) 0.09 (1–18 years)
Aqueous solubility (mg/mL)	250/15.79
Dissolution	Direct input of dissolution profiles for oral solid dosage forms
Absorption	
Effective permeability (P_{eff}) (cm/s)	$1.01*10^{-4}$

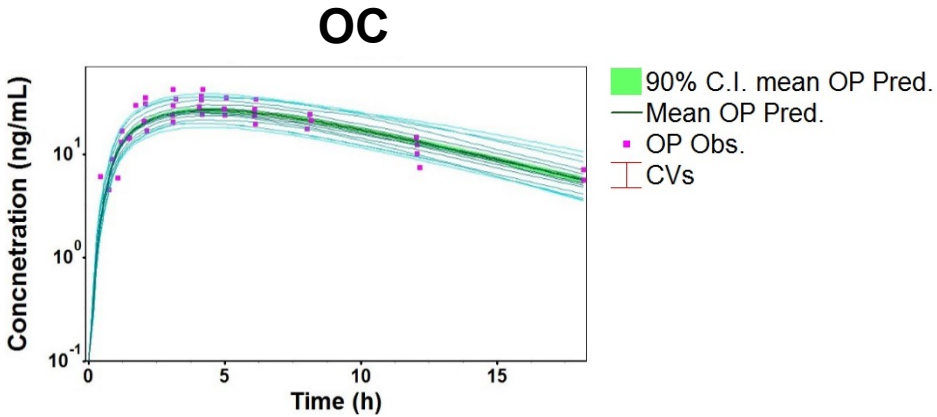


Miao L, Mousa YM, Zhao L, Raines K, Seo P, Wu F. Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations. AAPS J. 2020 Aug 10;22(5):107.

PBPK Model for Intravenous OP

- GastroPlus™ with PBPKPlus™ module was used for modeling and simulation
- **15 mg intravenous OP**





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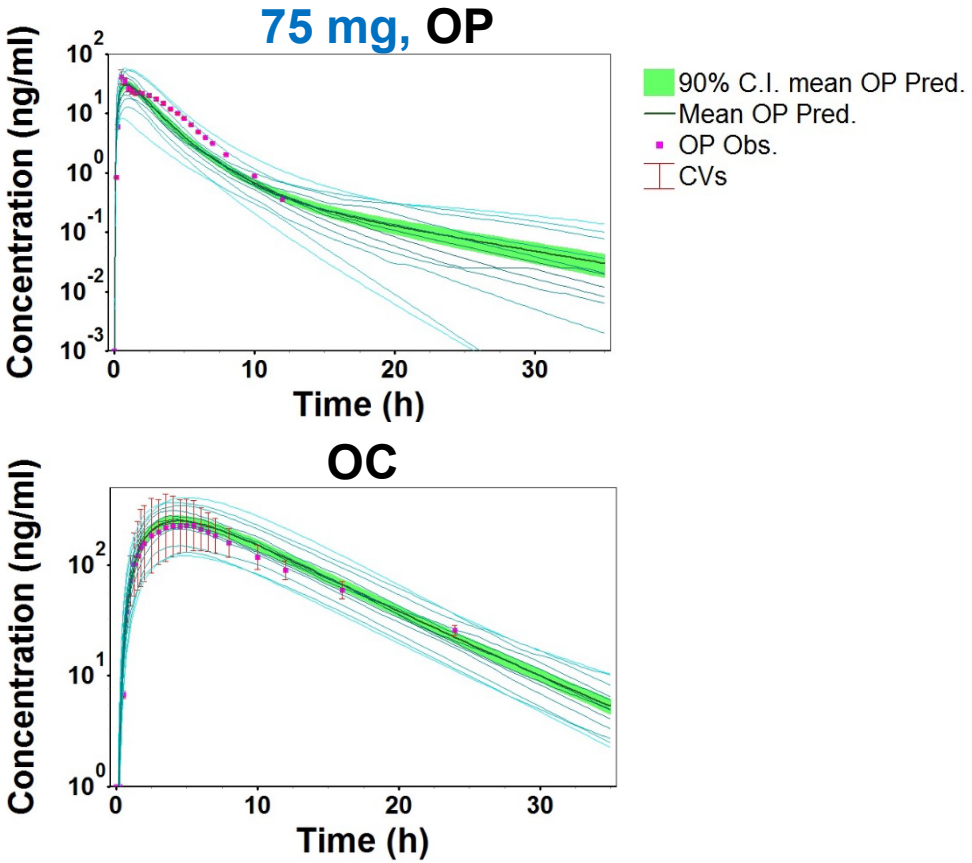
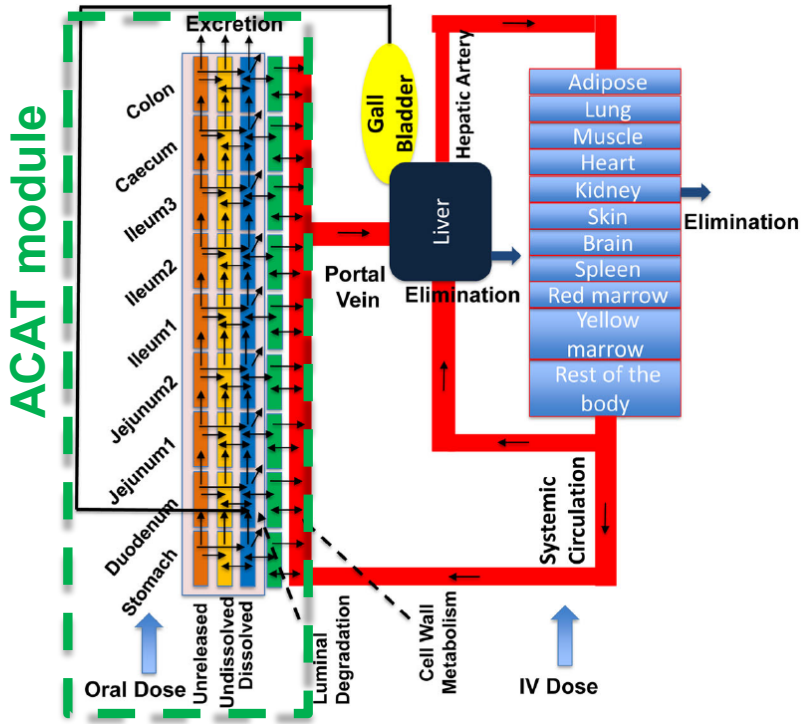
PBPK Model for Oral OP





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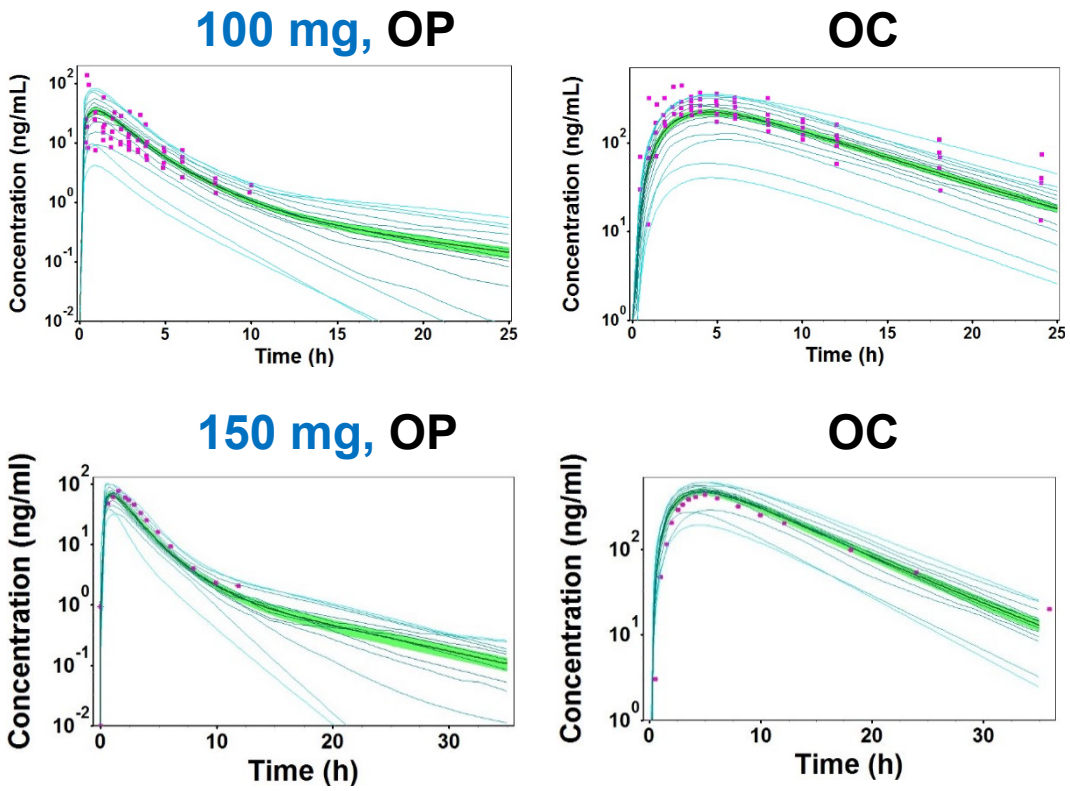
Validation of PBPK Model for Oral OP



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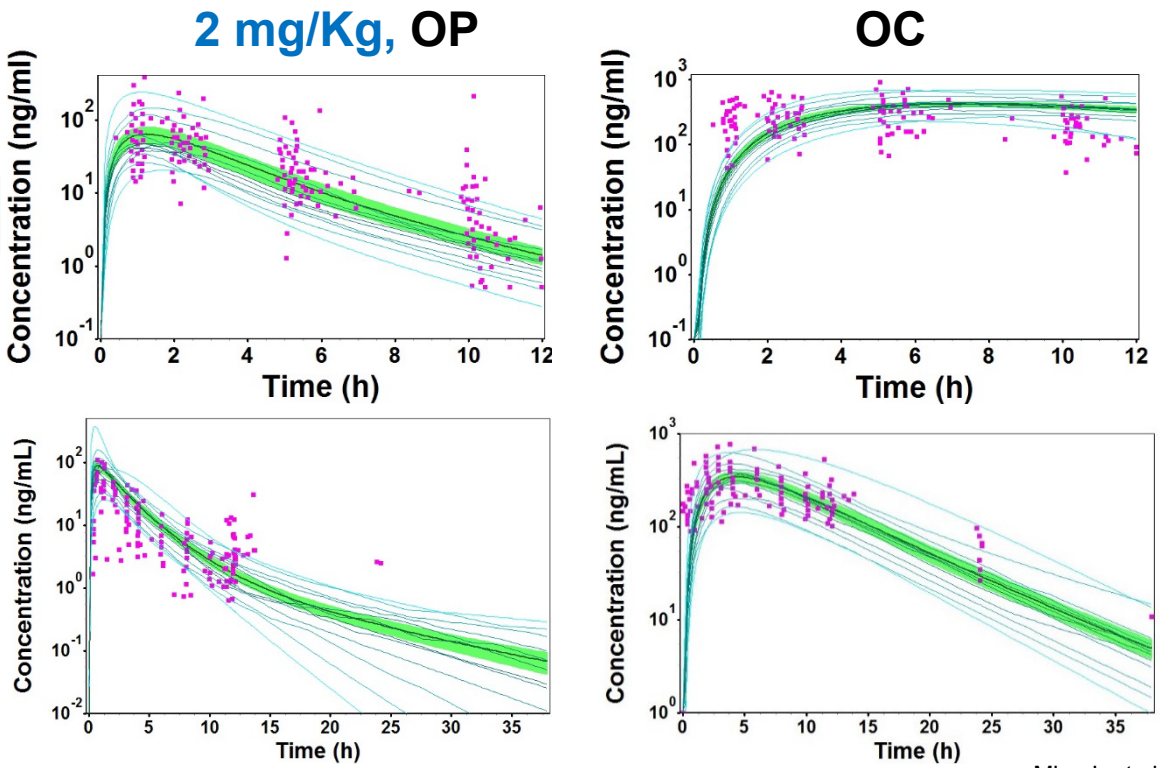
Predicting the PK Profiles in Pediatrics

0 – 2 months

9 – 18 years



The pediatric model was also validated in age groups 3 – 9 months and 1 – 5 years

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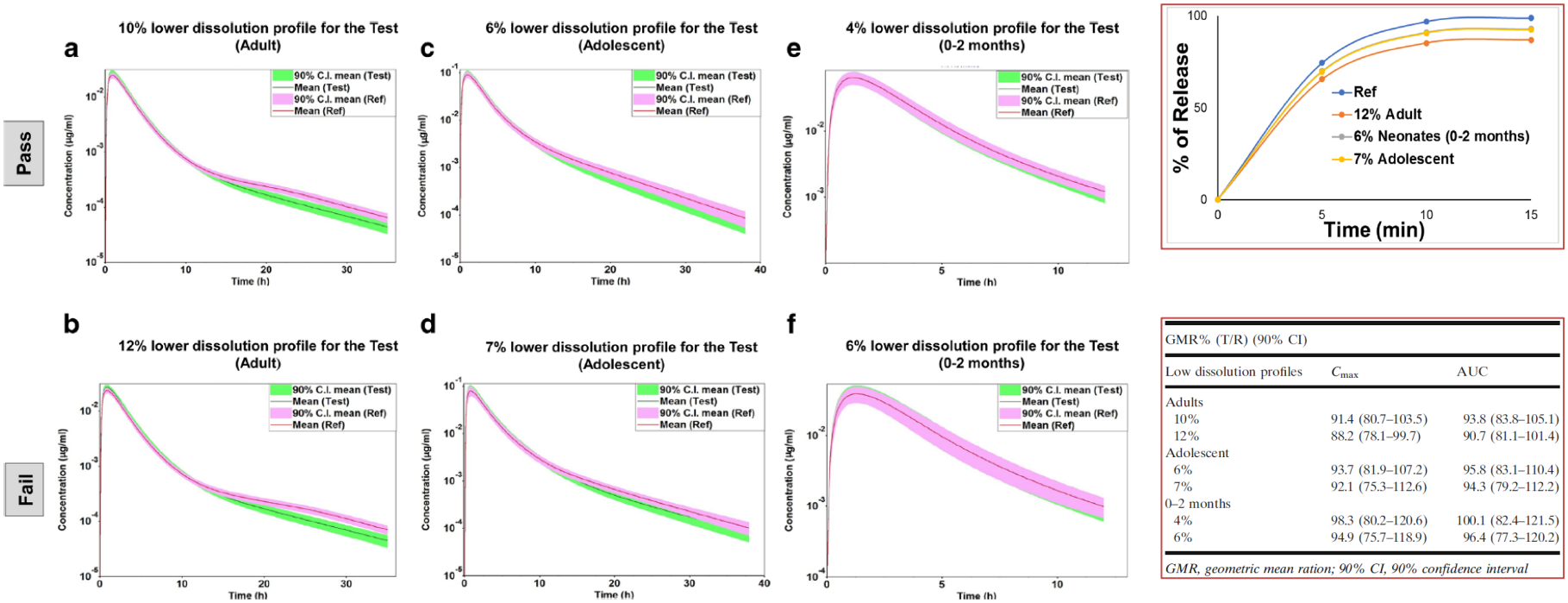
Virtual BE Simulation and Analysis for the Reference and Test OP Products in Adults and Pediatrics to Determine BE Dissolution Safe Space for OP



GMR% (T/R) (90% CI)		
Low dissolution profiles	C_{max}	AUC
Adults		
10%	91.4 (80.7–103.5)	93.8 (83.8–105.1)
12%	88.2 (78.1–99.7)	90.7 (81.1–101.4)
Adolescent		
6%	93.7 (81.9–107.2)	95.8 (83.1–110.4)
7%	92.1 (75.3–112.6)	94.3 (79.2–112.2)
0–2 months		
4%	98.3 (80.2–120.6)	100.1 (82.4–121.5)
6%	94.9 (75.7–118.9)	96.4 (77.3–120.2)

GMR, geometric mean ration; 90% CI, 90% confidence interval

Miao L et al. AAPS J. 2020 Aug 10;22(5):107

Case Example Summary

- The virtual BE analysis indicated that drug products with the dissolution boundary at 10% slower than dissolution profile of pivotal bio-batch could maintain BE to the reference listed drug in adults.

- In contrast, a stringent trend of dissolution boundary (safe space) was observed for pediatrics (6% slower for 8- to 18-year-old adolescents, 4% slower for neonates).

- This study highlights the utility of PBPK absorption modeling and simulation in prediction of BE and providing a quantitative basis for setting clinically relevant specifications for dissolution for OP in both adults and pediatric populations.

Miao L, Mousa YM, Zhao L, Raines K, Seo P, Wu F. Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations. AAPS J. 2020 Aug 10;22(5):107.

Challenges and Opportunities
Developing and Applying PBPK absorption Models for Pediatrics

Current status

- Drug substance and product attributes such as solubility, permeability, dissolution profiles, and particle size are used as pediatric model inputs

- Some system-dependent parameters, e.g., gastrointestinal (GI) pH, transit times, fluid volume, surface area and length, and enzyme/transporter localization and abundance are used as pediatric model inputs with assumptions

Further Improvement

- Consistent and adequate approach of generating (biorelevant) solubility, dissolution profiles, permeability, and particle size changes during the possible precipitation process is needed

- Uncertain system-dependent parameters need adequate justifications

Challenges and Opportunities
Developing and Applying PBPK absorption Models for Pediatrics

Current status

- Population predictions with generalized variabilities are used in PBPK model
- Validation/verification of PBPK model is conducted before the application of the model
- Limited application of PBPK modeling for pediatric products

Further Improvement

- Subject variabilities in pediatric population should be considered when needed
- Sufficient purpose-dependent model validation/verification is needed
- Application of PBPK modeling for pediatrics products can be used for BE or relative bioavailability assessment when appropriate

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

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DOI: 10.1208/s12248-020-00493-6

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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]

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]

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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,*]

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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]

Biopharmaceutics & Drug Disposition

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Fang Wu, Rodrigo Cristofoletti, Liang Zhao , Amin Rostami-Hodjegan

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REVIEW

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

Fang Wu[1] | Youssef Mousa[1] | Kimberly Raines[2] | Chris Bode[3] | Yu Chung Tsang[4] | Rodrigo Cristofoletti[5] | Hongling Zhang[6] | Tycho Heimbach[7] | Lanyan Fang[1] | Filippos Kesisoglou[7] | Amitava Mitra[8] | James Polli[9] | Myong-Jin Kim[1] | Jianghong Fan[10] | Banu S. Zolnik[2] | Duxin Sun[11] | Yi Zhang[1] | Liang Zhao[1]

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