

GastroPlus[®] PBBM/PBPK modeling: supporting R&D through regulatory interactions...

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Evolving relationship between in silico tools and R&D

- Model "supported" (first questions 20 years ago): Do you think modeling and simulation might help?
- Model "based" (current questions today): How can I maximize the value of modeling and simulation in my development program?
- Model "driven" (current & future questions): How do I change the R&D process to reflect the availability of *in silico* tools and techniques?



What a great time to be a PBBM/PBPK modeler!





St SimulationsPlus SCIENCE + SOFTWARE = SUCCESS

Peer-reviewed publications citing GastroPlus applications





The regulatory push...

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

https://www.fda.gov/media/101469/download

- ALECENSA[®] (absorption/PPI DDI)
- BRAFTOVI® (metabolism DDI)
- CALQUENCE[®] (particle size specs)
- FARYDAK[®] (food effect/PPI predictions)
- INLYTA[®] (transporter DDI)
- MEKINIST[®] (transporter DDI)
- MEKTOVI® (metabolism DDI)
- OPSUMIT[®] (particle size specs)
- TAMIFLU[®] (pediatric dose selection)
- ZURAMPIC[®] (wider product specs)
- ... and more!



2020 generic drug company survey

- Surveyed >30 generic drug companies licensing GastroPlus and/or working with our consulting teams
- Invited responses to:
 - Guide GastroPlus R&D activities heading into 2021
 - Describe use cases and regulatory interactions with GastroPlus
- Several questions included:
 - Which new formulation type would you find most useful in GastroPlus?
 - Which new population group would you find most useful to assist with virtual BE trials in GastroPlus?

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Approved to support regulatory claim(s)

Please indicate your company's experience on the use of GastroPlus for regulatory submissions (e.g. ANDAs)? (check all that apply)





PBBM/PBPK modeling to support regulatory interactions: New guidance documents!

The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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 <u>https://www.regulations.gov</u>. 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 Paul Seo at 301-796-4874.

https://www.fda.gov/media/142500/download

Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

Physiologically based PK simulations: In conjunction with the assessment framework
outlined in Figure 1, physiologically based PK (PBPK) simulations can sometimes be
used to further assess the potential for pH-dependent DDIs. PBPK approaches can also
be useful to inform clinical study designs. The application of PBPK is still evolving, and
new applications of PBPK simulation are continuously being evaluated by the FDA.
Therefore, sponsors are encouraged to consult the appropriate review division.

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only. https://www.fda.gov/media/144026/download



Outline

- How is GastroPlus[®] structured?
- How is GastroPlus[®] applied to support oral product development?
- Conclusions



What's happening in vivo?







Advanced Compartmental Absorption and Transit Model (ACAT™)



Validated system models in GastroPlus[®]



The Big Picture – small molecule inputs





Discovery

Preclinical

Clinical



Discovery PK

Combine *in silico* technologies to screen compound libraries in animals or humans

Incorporate preclinical/in vitro data to extend FIH simulations to full in vivo outcomes (IVIVE)

Identify toxic dose levels in preclinical species

<u>Clinical PK/Pharmacology</u> Simulate population behaviors (e.g., pediatrics, disease) Build PBPK-PD models Predict DDIs

Pharmaceutical Development

Assess various strategies during formulation development Assist with Quality by Design (QbD) implementation Develop mechanistic *in vitro-in vivo* correlations (IVIVCs) Understand food effects



Biopharmaceutical risk assessment program



Pharmaceutical risk assessment strategy



Two step assessment program:

In silico model (in view of human situation)

(2) In vivo studies (animal model) where experimental formulations (maximal biopharm. difference targeted) are tested in a statistical design

- Critical parameters for a formulation can be identified before starting any in vivo work
 - Sensitivity analysis helps guide resource placement
- Assist with Quality by Design (QbD) implementation •



Kuentz et al. Eur. J. Pharm. Sci. 2006. 27:91-99.

R1315 PSA for particle size and solubility



- 12 total simulations were run to assess the sensitivity of bioavailability to changes to particle size and solubility
 - − 0.5 um \leq particle size \leq 50 um
 - $0.002 \text{ mg/ml} \le \text{solubility} \le 0.2 \text{ mg/ml}$
- Results indicate that particle size reduction or solubility enhancement by technological means may not lead to improved absorption or higher bioavailability



Comparison of simulated results with measured data for R1315



Fig. 7 – Plasma levels of individual dogs that received a solution. Diamonds hold for profiles of 2 mg/kg dose, whereas those of the 4 mg/kg dose are represented by squares. The light symbols hold for the fasted condition and the bold symbols for fed dogs.



Fig. 8 – Plasma levels of individual dogs that received a capsule. Diamonds hold for profiles of 2 mg/kg dose, whereas those of the 4 mg/kg dose are represented by squares. The light symbols hold for the fasted condition and the bold symbols for fed dogs.

- Based upon the predictions from GastroPlus[™], in vivo dog studies were performed using two different formulations
 - "Best" formulation: Cremophor vehicle solution
 - "Worst" formulation: Pure drug substance in capsule
- While the variability is high, there is no significant difference in AUC between the two formulations



Biorelevant dissolution to guide formulation switch



- BCS Class II compound from Sun Pharmaceuticals:
 - Practically insoluble in water
 - pKa: Base = 2.66, Acid1 = 9.02, Acid2 = 9.73
 - Log D: 3.27 @ pH 7.45
 - Permeability (Caco-2): 3.5 × 10⁻⁶ cm/sec
- **Product design:** Enabling formulation for improved solubility and oral bioavailability
- **Study objective:** Identify a biorelevant dissolution condition for screening formulations for formulation switch



- Does the capsule release completely in vivo?
- Is there any possibility of *in vivo* precipitation?
- Is the QC method under/over discriminatory?





- Mechanistic deconvolution based on GastroPlus ACAT[™] model coupled with systemic PBPK model:
 - *in vivo* precipitation followed by slow and sustained dissolution
 - C_{max} results from dissolution of only 20-40% of drug
- Biorelevant dissolution method:
 - Non-sink conditions
 - Optimization of tablet formulation for bridging study based on target deconvoluted profile from GastroPlus





Ketkar A. SPDS 6th International Annual Symposium on Dissolution Science and Applications (2018)

• Bridging PK study results:

- Tablet was bioequivalent to capsule





Understanding food effects to guide formulation development



Fed State – GI physiology

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SCIENCE + SOFTWARE = SUCCESS

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Analyzing multiple dimensions: Design of Experiments (DoE) approach

Parameters	Value(s)
Compound parameters	
M _w : g/mol	>475
cLogP:	>4
pK_a (base):	3.2, 6.2
Dosage:	IR capsule
Solubility (mg/mL):	1.8 (pH 1), 0.3 (pH 2), 0.001 (pH 6.8)
Biorelevant solubility (mg/mL):	0.023 (fasted); 0.190 (fed)
Mean precipitation time (s) :	450 s (fasted); 2,000 s (fed)
Effective permeability (cm/s):	1.48×10^{-4}
Particle radius of API (µm):	19
Physiological parameters	
Stomach pH	1.2 (Fasted); 1.2-4.9 (Fed)
Duodenum/jejunum pH	6.0-6.4 (Fasted); 5.4-6.0 (Fed)
Ileum pH	6.6-7.4 (Fasted); 6.6-7.4 (Fed)
Cecum-colon pH	6.4-6.8
Stomach transit time (h)	2.0 (Fasted); 5.4 (Fed)
Small intestine transit time (h)	3.3
Cecum transit time (h)	4.2
Ascending colon transit time (h)	12.6
Pharmacokinetics	
First pass extraction (%):	9.0
Blood/plasma ratio:	0.68
Plasma unbound (%):	1.6
Clearance (L/h/kg)	0.070
V_c (L/kg)	0.4
$k_{12} (1/h)$	0.64
k_{21} (1/h)	0.17
V_t (L/kg)	1.5



- Baseline models in GastroPlus were developed to predict the food effect for a weak base compound across different doses
- Is there an optimal combination of formulation parameters that allow us to reach our target endpoint (e.g., Fa%, Cmax, AUC)?

3D Parameter Sensitivity Analysis



- Parameter sensitivity analysis was run across dose and particle size together
- API particle size reduction may be useful to mitigate the food effect



Food effect projections via PBPK modeling: Predictive case studies





Virtual crossover trials to show BE and establish particle size specification after manufacturing changes



M&S objectives

- Post approval, sponsor's manufacturing process change resulted in different particle size distributions for new lots
 - Inline milling step added to crystallization process (PE)
- With GastroPlus, could they apply for a biowaiver by:
 - assessing the effects of changes in particle size distribution of the active pharmaceutical ingredient (API) on its oral bioavailability?
 - predicting the virtual bioequivalence between the "new" and "old" API lots?



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Proposed modeling tasks

- Part I: determine the most appropriate absorption/PBPK model for the API across several doses for the non-engineered lots
- **Part II:** assess the effect of particle size on API exposure for the immediate release formulation
- **Part III:** evaluate predicted bioequivalence of the tablets manufactured with particle-engineered (PE) API (narrower particle size distribution) versus the tablets manufactured with non particle-engineered (NPE) API (broader particle size distribution)



Part I: Building the baseline model: Key modeling parameters

- BCS Class IV drug
- Neutral compound
- Aqueous solubility = 10 μg/mL
- Significant solubilization by bile salts
- Intermediate lipophilicity
- No food effect

Parameter	Value
CL	0.115 L/h/kg
First pass extraction	17%
Vc	0.324 L/kg
K12	0.26 h ⁻¹
K21	0.1 h ⁻¹

Various Particle Size Used in Clinical Studies

NPE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)	PE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)
NPE Lot 1	20	63	173	PE Lot 1	16	40	88
NPE Lot 2	8	179	512	PE Lot 2	20	49	102
NPE Lot 3	15	49	142	PE Lot 3	22	53	108
NPE Lot 4	31	86	348	PE Lot 4	19	39	71
NPE Lot 5	26	78	276	PE Lot 5	17	35	67
NPE Lot 6	9	29	101	PE Lot 6	23	48	93
NPE Lot 7	11	35	114	PE Lot 7	21	44	87
NDE Lot 9	12	27	124	PE Lot 8	21	45	90
NPE LOU 8	12	37	124	PE Lot 9	24	50	94
NPE Lot 9	10	36	119	PE Lot 10	21	45	89
NPE Lot 10	13	45	138	PE Lot 11	19	42	88
NPE Lot 11	11	35	99	PE Lot 12	22	47	95

API: active pharmaceutical ingredient; d10, d50, and d90: diameter for which 10%, 50%, and 90% (respectively) by volume of the particles are less than this value NPE: non-particle-engineered; PE: particle-engineered

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Instrumt 0 2.589 7.40 0.29 53.57 60.26 0.84 2.109 0.140 Caecum 0 0.352 6.40 4.36 50.49 13.50 3.45 1.730 0.0 Vac Colon 0 0.823 6.60 13.07 53.55 28.35 2.450 0.0	2 0	2.1	.621 6	6.90	0.42	75.35	60.26	1.00	2.569	1.160		
Casecum 0 0.352 6.40 4.36 50.49 13.50 3.45 1.790 0.0 Ase Colon 0 0.823 6.80 13.07 53.55 28.35 2.45 2.480 0.0	3 0	2.5	.589 7	7.40	0.29	53.57	60.26	0.84	2.109	0.140		
Ase Colon 0 0.823 6.80 13.07 53.55 28.35 2.45 2.480 0.0	m O	0.3	.352 6	6.40	4.36	50.49	13.50	3.45	1.790	0.0		
	olon 0	0.3	.823 6	6.80	13.07	53.55	28.35	2.45	2.480	0.0		
										Þ		
C1-C4: 0.06944 0.43028 0.12147 0.46632 Qh (L/min):	: 0.06944	4	0.430	28	0.12	147	0.466	32			Qh (L	/min):
Physiology: Human - Physiological - Fasted Percent Fluid in SI: 40 Colo	hysiology:	Human -	Physiolog	gical - Fa	asted				•		Percent Fluid in SI: 40	Colon: 10



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Part I: Simulation results for baseline models of non-engineered lots



Total simulation	tir	ne (ł	1): 24		
Result (Jbs	serv	9	Simu	l
Fa (%)	_	0	85.	907	
FD _D (%) ———	-	0	85.	907	
F (%)0	_	0	71.	303	
Cmax (ng/mL):_	_	391.	2	3	99.12
Tmax (h):	_	1.5		:	2.56
AUC o-inf (ng-h/n	nL)	356	3.7	3	739.6
AUC o-t (ng-h/mL)):_	313	9.1	3	3702
Cmax Liver (ng/m	L):			53	1.85



Total simulatio	n tir	ne (h)	: 24	
Result	0bs	erv	Sin	nul
Fa (%)		0	96.42	2
FD _D (%)	_	0	96.42	2
F (%)0	_	0	80.03	
Cmax (ng/mL):		2768		3245.8
Tmax (h):		1.5		2.08
AUC o-inf (ng-h/	mL)	26290	D	24970
AUC o-t (ng-h/m	L):_	22590)	20990
Cmax Liver (ng/	mL):			4079.7



Result	0bs	erv	Sim	ul
Fa (%)		0	85.90	7
FD _D (%)		0	85.90	7
F (%)0		0	71.30	3
Cmax (ng/n	1L):	926.3		399.12
Tmax (h): _		1.5		2.56
AUC o-inf (n	g-h/mL)	7545	.6	8462.2
AUC o-t (ng-l	h/mL):_	6358.	8	7117.3
Cmax Liver (ng/mL):			1385.9

Same baseline absorption model does a good job of predicting the observed plasma concentrationtime data across the three different doses of the NPE ("old") API lots.



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Part II: Parameter Sensitivity Analysis (PSA) around mean particle radius: Dose range: 10 – 1000 mg



- ▲ 10 mg
 △ 20 mg
 ◆ 50 mg
 ◊ 100 mg
 ◊ 200 mg
- * 500 mg
- 1000 mg

PSA was used to establish particle size specifications.

Results indicated that there would be small changes in Fa% until the largest particle sizes of the NPE API lots (> 30 - 40 μ m) were reached *and* the dose exceeded 100 mg.



Part II: Parameter Sensitivity Analysis (PSA) around standard deviation & shape factor: Dose range: 10 – 1000 mg

PSA was also run to evaluate changes in particle size standard deviation (assuming mean remained constant) and particle shape factor

Results indicated that there would be insignificant/moderate changes in Fa% across the range of values evaluated



Part III: Virtual bioequivalence trials: Population Simulator™

Incorporate measured variability for physicochemical, formulation, physiology and PK parameters into Population Simulator

Capture observed variability from existing clinical PK studies

Clea <u>r</u> All Add <u>A</u> ll Add <u>S</u> elect Set Defaults	 Dose of Valsartan (mg) Primary Permeability of Valsartan (c Particle Character (C) (closeter) 	91.514	100			
Add <u>A</u> ll Add <u>S</u> elect	Primary Permeability of Valsartan (c		100	109.27	3	og-Normal
Add <u>A</u> ll Add <u>S</u> elect	Destinia Change Frankes of Valuesters	0.2048	0.92	4.1328	65	og-Normal
Add Select	Farticle Shape Factor or Valsartan	0.7513	1	1.331	10	og-Normal
Add <u>S</u> elect	Mean Drug Particle Radius of Valsa	18.783	25	33.275	10	og-Normal
Add <u>S</u> elect	Precipitation Particle Radius of Vals	0.7513	1	1.331	10	og-Normal
Set Defaults	Precipitation Time of Valsartan (sec	676.18	900	1197.9	10	og-Normal
Set Defaults	Reference Solubility of Valsartan (rr	0.0738	0.0982	0.1307	10	og-Normal
	Fraction Unbound in Enterocytes o	0.7513	1	1.331	10	og-Normal
	Oral Transit Time of Valsartan (h)	0.1878	0.25	0.3328	10	og-Normal
	Oral Cavity ASF Valsartan	0.7513	1	1.331	10	og-Normal
Population –	Duodenum ASF Valsartan	2.1011	2.7965	3.7221	10	og-Normal
	Jejunum 1 ASF Valsartan	2.0672	2.7514	3.6621	10	og-Normal
Set <u>P</u> EAR	Jejunum 2 ASF Valsartan	2.0506	2.7294	3.6328	10	og-Normal
	lleum 1 ASF Valsartan	2.0273	2.6983	3.5914	10	og-Normal
Load Previous	lleum 2 ASF Valsartan	1.988	2.6461	3.522	10	og-Normal
	lleum 3 ASF Valsartan	1.9416	2.5843	3.4396	10	og-Normal
Create New	Caecum ASF Valsartan	0.0797	0.1061	0.1412	10	og-Normal
	Asc Colon ASF Valsartan	0.1551	0.2064	0.2747	10	og-Normal
F	OralMucosaVolume (mL)	2.6296	3.5	4.6585	10	og-Normal
Г	SalivaProductionRate (mL/min)	0.7513	1	1.331	10	og-Normal
-	Fraction of colon fluid volume in fas	7.5131	10	13.31	10	og-Normal
F	Fraction of SI fluid volume in fasted	30.053	40	53.24	10	og-Normal
	Small Intestine Length (cm)	230.01	306.14	407.47	10	og-Normal
F	Caecum Length (cm)	9.9118	13.193	17.559	10	og-Normal
F	Colon Length (cm)	20.772	27.648	36.799	10	og-Normal
Г	Stomach Volume (mL)	34.981	46.56	61.972	10	og-Normal
F	Small Intestine Radius (cm)	0.7513	1	1.331	10	og-Normal
-	Caecum Radius (cm)	2.5433	3.3851	4.5056	10	og-Normal
-	Colon Radius (cm)	1.8086	2.4073	3.2041	10	og-Normal
F	Stomach Transit Time (h)	0.1447	0.25	0.432	20	og-Normal
F	Small Intestine Transit Time (h)	1.857	3.2088	5.5448	20	og-Normal



Mean Cp
 90% Percentile
 Observed Individual Data



Virtual Bioequivalence Study Simulations

API Lot	API Lot PE/NPE		AUG	C _∞ (ng.h/mL) (N=250)	C _{max} (ng/mL) (N=250)			
		(mg)	GM	GMR (90% CI)	GM	GMR (90% CI)		
Lot 5	PE	50	4180	113.3	551	139.3		
Lot 1	NPE	50	3688	(110.7, 116.1)	395	(136.0, 142.7)		
Lot 5	PE	100	8242	103.0 (100.9, 105.1) 102.2	551	106.4		
Lot 3	NPE	100	8001		395	(104.3, 108.6)		
Lot 5	PE	300	24998		3118	100.0		
Lot 2	NPE	300	24460	(99.8, 104.6)	3117	(97.7, 102.4)		
Lot 5	PE	100	8242	98.2	1068	95.1		
Lot 4	NPE	100	8395	(96.2, 100.2)	1123	(93.2, 97.0)		
Lot 5	PE	300	24998	101.9	3118	98.3		
Lot 4	NPE	300	24525	(99.8, 104.1)	3171	(96.3, 100.4)		

API: active pharmaceutical ingredient; AUC_w: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ration; NPE: non-particle-engineered; PE: particle-engineered



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Summary

- A mechanistic, physiologically-based absorption/PK model was constructed in GastroPlus and validated across three dose levels (50, 100, and 300 mg) using *in vivo* data collected from tablets manufactured with non particle-engineered API.
- Parameter sensitivity analysis showed that mean particle size would be the main property that determines whether formulations are likely to be bioequivalent, regardless of dose.
- Virtual bioequivalence trial simulations showed that, for a sufficiently powered study, the population-derived C_{max} and AUC values would be bioequivalent between the tablets manufactured with non particle-engineered (NPE) vs. new particle-engineered (PE) API, up to 40 µm particle size, regardless of the dose.
- Regulatory agencies approved the sponsor's biowaiver application
- Sponsor got to market ~12 months before it would have running the full trials



Conclusions



How PBBM/PBPK modeling & simulation can save resources in R&D

- Prioritize experiments to be done **better invest resources**
- Integrate the wide variety of data obtained from *in silico, in* vitro and *in vivo* experiments to tell a compelling story
- Reduce regulatory burden
- Productivity tools be the first to market



SI SimulationsPlus

Cognigen DILIsym Services Lixoft

www.simulations-plus.com

Products & Services

Software Portfolio

- PBBM/PBPK modeling & simulation platform for R&D
- Machine learning technology for ADMET endpoints
- QSP/QST software for certain biological or disease states
- Population PK/PD functionality for pharmacometricians

Consulting Services

 Provide multi-disciplinary modeling and simulation support from discovery through post approval

Corporate Information

- Company founded in 1996 and now has >130 employees worldwide.
- Primary offices located in Los Angeles, CA; Buffalo, NY; Raleigh, NC; and Paris, France

Operating Divisions

- Simulations Plus, Inc.
- Cognigen Corporation
- DILIsym Services
- Lixoft

Consistent Financial Results/Investments

- Publicly traded (NASDAQ: SLP)
- > 10 years of consistent revenue growth
- > 10 years of profitability
- Invest ~10% of revenue into software R&D

Customers and Market

- >250 pharmaceutical, biotechnology, chemicals, and consumer goods companies in the U.S., Europe, Asia, and South America
- Most major regulatory agencies (U.S. FDA, EMA, PMDA, NMPA, Health Canada) have reviewers trained on our technology
- >1000 peer-reviewed journal articles and conference presentations citing software



>1100 members on the LinkedIn group page – membership is free!

GastroPlus® User Group on LinkedIn

Mission & Goals:

Discuss best practices, Q&A and FAQs Share knowledge of software functionality and applications Publish journal articles to show validation for different applications Present and advance M&S science via social media, webinars and face-to-face meetings Feedback on improvements and software functionality requests to Simulations Plus Understand and influence regulatory expectations for M&S submissions

