

Generics for emerging markets and beyond

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.

Harnessing the Power of Emerging Markets: A Pharmaceutical Industry Opportunity



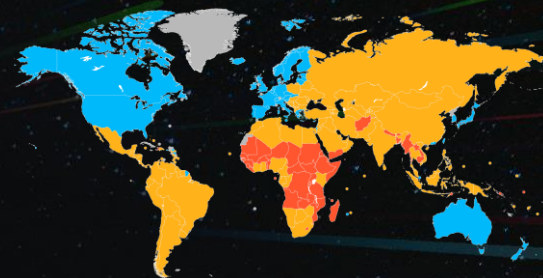
Emerging markets represent a great opportunity for the pharmaceutical industry.



BRICS, followed by MIST, are leading economies of emerging markets.



Sales of pharmaceutical markets in BRICS and MIST countries doubled in 5 years and reached 20% market share



BRICS is an acronym for five leading emerging economies: **Brazil, Russia, India, China, and South Africa.**

MIST is an acronym for: **Mexico, Indonesia, South Korea, and Turkey**

Empowering Emerging Economies: The Benefits of Generic Medications

The genesis of branded generics in emerging markets is a pragmatic response to some hard local market realities.

Affordability and Cost-Effective : Generics are more affordable and accessible to a wider range of patients.

Boost to Local Economy: The production and sale of generic drugs can provide a boost to the local economy in emerging countries, creating jobs and contributing to economic growth.

Overcoming Hurdles to Successfully Launch Generic Medications in Emerging Markets

- The market for generic medications is highly competitive, with numerous companies vying for a share of the growing demand for affordable alternatives to brand-name drugs.



Revolutionizing Generic Drug Development with Model-Informed Approaches



SLP University+ Program

Offering free access to Simulations Plus software to universities worldwide

Get your hands on the tools that allow you to run additional simulations or studies.

Consult + Coach

Accelerate Your Program and Invest In Your Future

SimulationsPlus G+

GastroPlus®

Accelerate your company's goals by using models built by our experts!

Convenience

Click File → Load and away you go!

Confidence

Validated GastroPlus® model packages developed and reviewed by expert modelers and regulatory gurus.

Advantage

Get to market sooner by reducing the time it takes to develop baseline models.

The GastroPlus® Plug n' Play PBBM Packages

simulations-plus.com/gastroplus

Connect with us:

SimulationsPlus

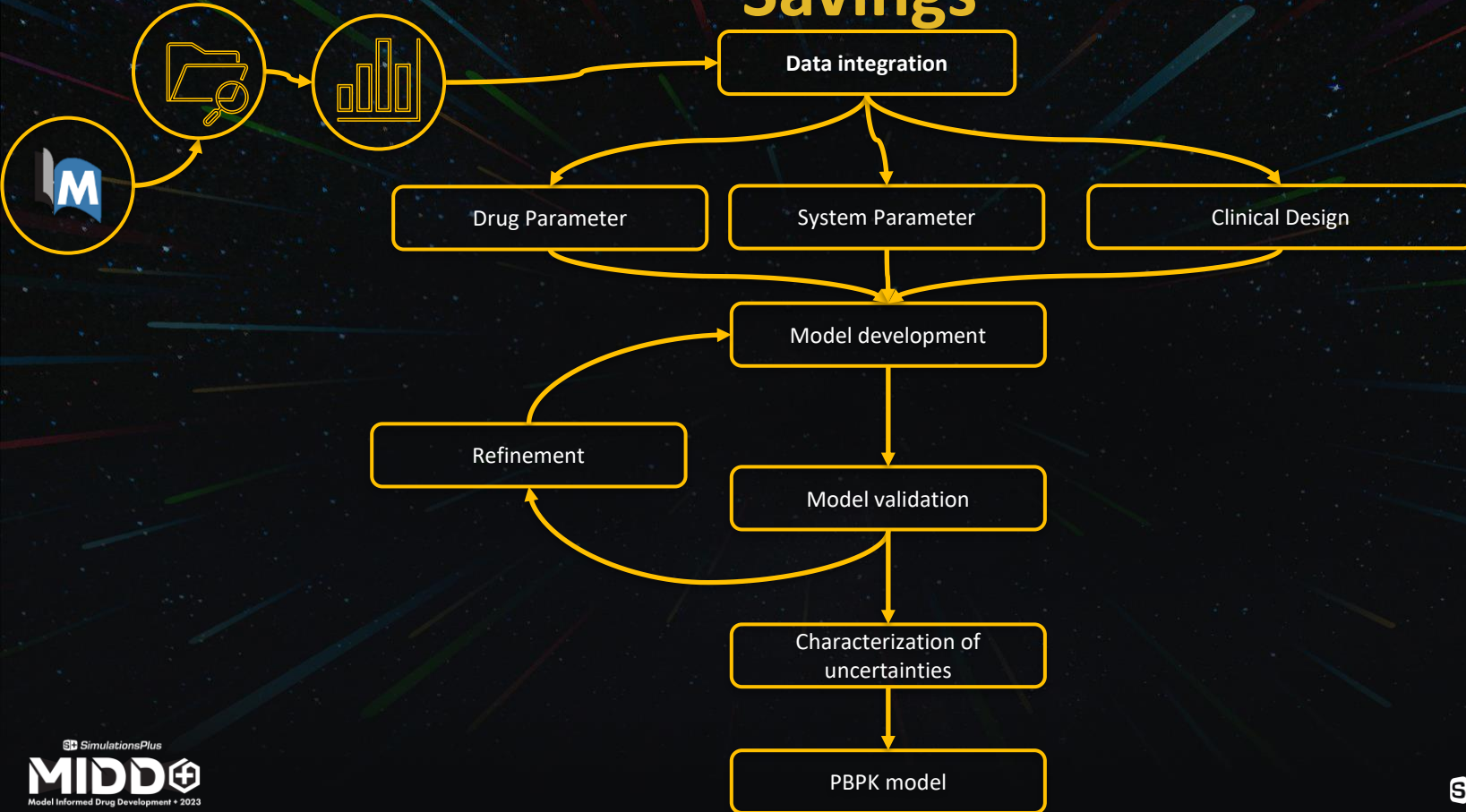
Simplify the Generic Drug Product Development Process

Three tiers of PBBM models

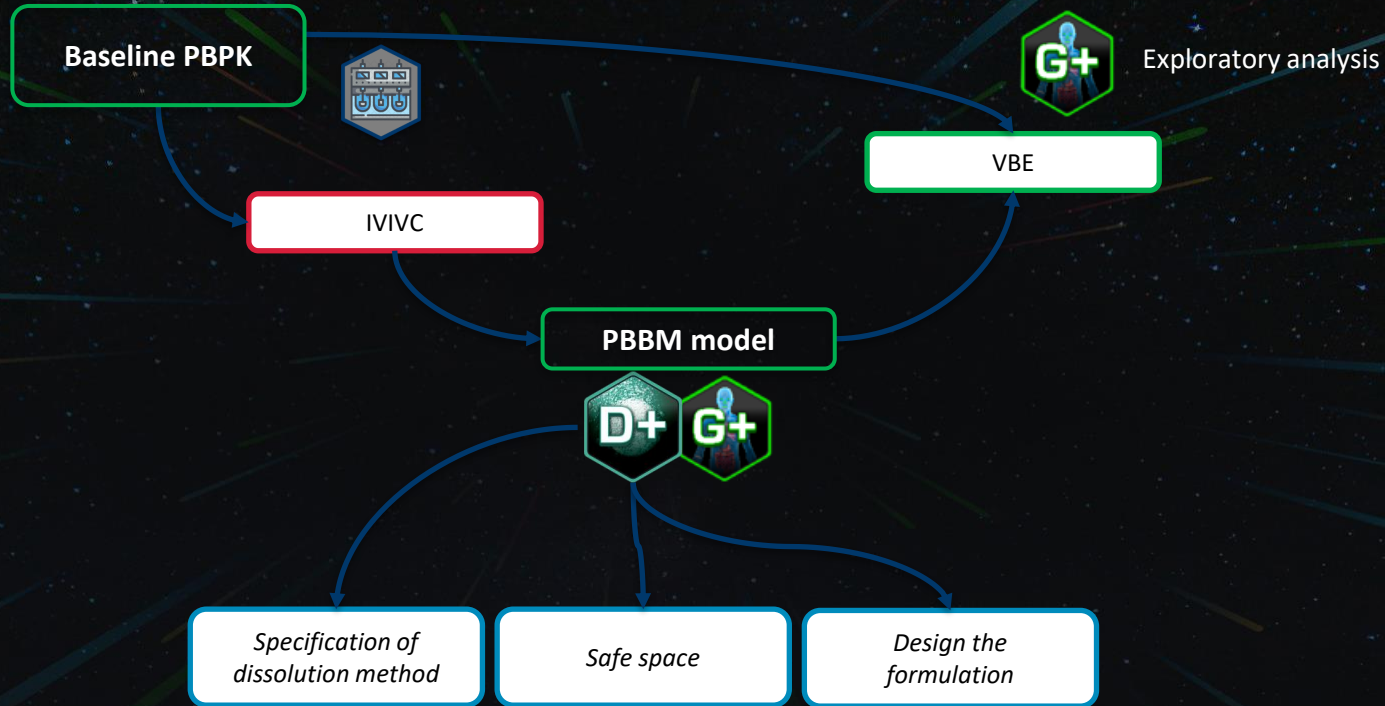
- Tier 1 – Metoprolol, Ibuprofen, Bupropion
- Tier 2 – Atorvastatin, Valsartan, Zolpidem, Ranitidine, Metformin, Repaglinide, Methylphenidate
- Tier 3 – Rivaroxaban, Apixaban



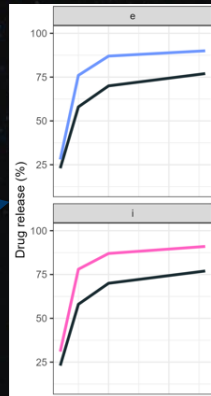
Achieving Success through Quality and Time Savings



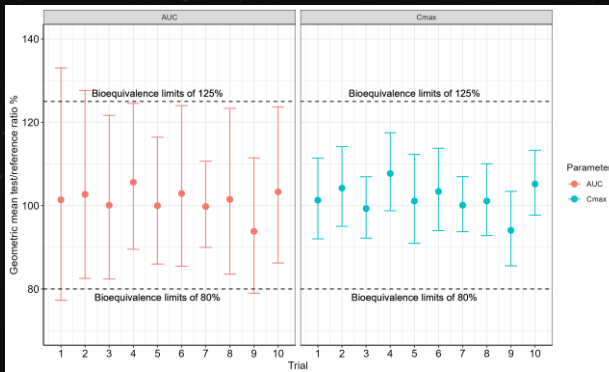
Achieving Success through Quality and Time Savings



How does Plug and Play work



vBE



What are the benefits of using Plug and Play?

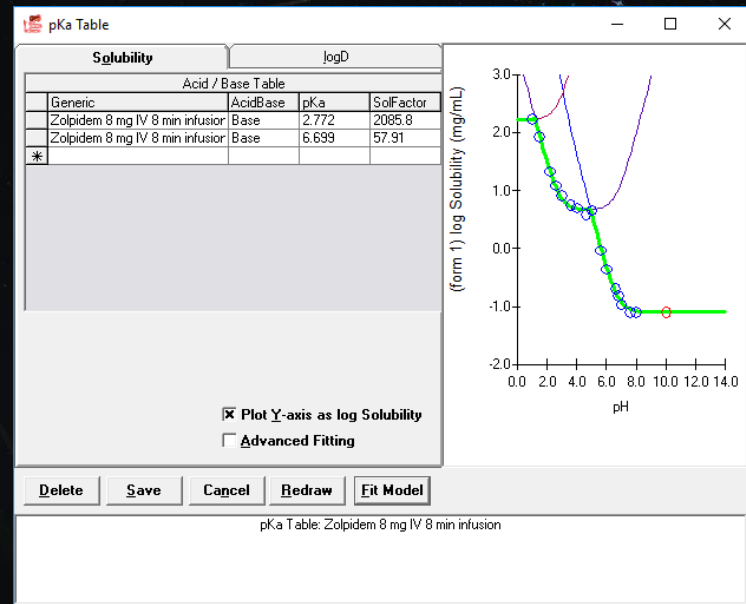
- Transform your analysis into a high-performance operation and reduce analysis time while increasing result accuracy.
- Reduce time and costs with data curation.
- Reduce costs and time with efficient training and professional development.
- Increase the efficiency of your R&D program.
- All models are qualified and pre-reviewed by experienced regulatory professionals to increase chances of success in submissions to regulatory agencies

Zolpidem ODT

Objective : Predict likelihood of clinical trial outcome (BE between test and reference product)

Zolpidem hemitartrate– Physico-chemical and biopharmaceutical properties

- MW = 764.88 g.mol⁻¹ (=307.4 for active moiety)
- Salt to base ratio = 1.24
- Caco2 scaled to human jejunal Peff = 4 x10⁻⁴cm/s
- fu,p = 7.5%, B:P = 0.76
- Log P= 2.42
- Weak base
 - pKa = 6.18
- Aqueous solubility
 - pH dependent
 - S₀ = 0.08 mg/mL @ pH 10



Zolpidem hemitartrate– Physico-chemical and biopharmaceutical properties

GastroPlus(TM): Zolpidem.mdb (C:\Users\kdn377\OneDrive\VAZ co.\Vclod.VHC in.\Train.VG+ mo.\)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Gut Physiology-Hum Pharmacokinetics Stimulation Graph

Selected Compound

ver: 9.7.0003
SI Trans Time (h) = 3.217 Mean Abs Time (h) = 0.404
Longest Diss. Time (h) is @ pH 6.8 = 0.026 hours
Max Abs Dose (S+) = 3.329E+3 mg Max Abs Dose (R) = 1.119E+3 mg
Support Files
Zolpidem tartrate 10 mg IR.opd Zolpidem tartrate 10 mg IR.spd

Current = 2, Total = 16

Molecular Formula: C₁₄H₂₂N₂O₃
Molecular Weight (g/mol): 307.4
logP (neutral): 2.42 @pH: 7.4

pKa Table

Enzyme Table

Transporter Table

Dosage Form: IR: Tablet
Initial Dose (mg): 8.04
Subsequent Doses (mg): 0
Dosing Interval (h): 0.5
Dose Volume (mL): 200

pH for Ref. Solubility: 10
Solubility (mg/mL @pH=10): 0.08
Mean Precipitation Time (sec): 10000
Diff. Coeff. (cm²/s x 10⁻⁵): 0.7581
Drug Particle Density (g/mL): 1.2
Particle Size (form 1): R=5.00, D=10.00

Effective Permeability
Source: **ADMET**
Peff (cm/s x 10⁻⁴): 4
Sim Peff x 10⁻⁴ (Human): 4.0
Convert from User Data

Bioequivalent Solubilities

Dose No. = 0.5

Absorption No. = 7.964

Dissolution No. = 1.258E+2

Notes
On 04/02/2016 some pKa values were fitted to experimental Solubility-pH profile and updated as:
Base pKa from 4.000 to 2.772 and its Solubility Factor from 50.00 to 2055.8
Base pKa from 6.180 to 6.696 and its Solubility Factor from 50.00 to 57.62
On 04/02/2016 some pKa values were fitted to experimental Solubility-pH profile and updated as:
Base pKa from 6.696 to 6.699 and its Solubility Factor from 57.62 to 57.91

pKa Table logD: Emp-6.1 Diss Model: Johnson PartSize Sol: OFF BileSaltSol: ON Diff: ON ConfRad: OFF Precip: Time Ppers: OFF EHC: OFF ACAT: Conc

Dissolution Model for: Zolpidem 8 mg IV 8 min infusion

Dissolution Model: Johnson Z-factor (mL/mg/s): 0 [Fit to In Vitro Data](#)

Effect of Temperature on Solubility
Ref Temp [degC]: 37 Melting Point [degC]: 0

Nanoparticle Effect
☐ Adjust solubility for nanoparticle effect
Nano Factor: 0.5 Interf tension (J/m²): 0.05

Bile Salt Effect
☒ Adjust solubility for bile salt effect
☒ Adjust diff coeff for bile salt effect
Solubilization Ratio (SR): 6924.3 [Fit to In Vitro Data](#)

☐ Use theoretical solubilization ratio

Bioequivalent In Vitro Solubilities
Use the bioequivalent solubilities of form 1
At least one of the FaSSIF, FeSSIF, or User solubilities must be specified to calculate solubilization ratio
Enter 0 for values of bioequivalent solubilities that are not available. Zero values are not used in SR calculation

	SGF	FaSSIF	FeSSIF	User
pH: 1.2	6.5	5.8	0	
Bile Salt Conc (mM): 0	3	10	0	
Solubility (mg/mL): 0	2.21	8.27	0	

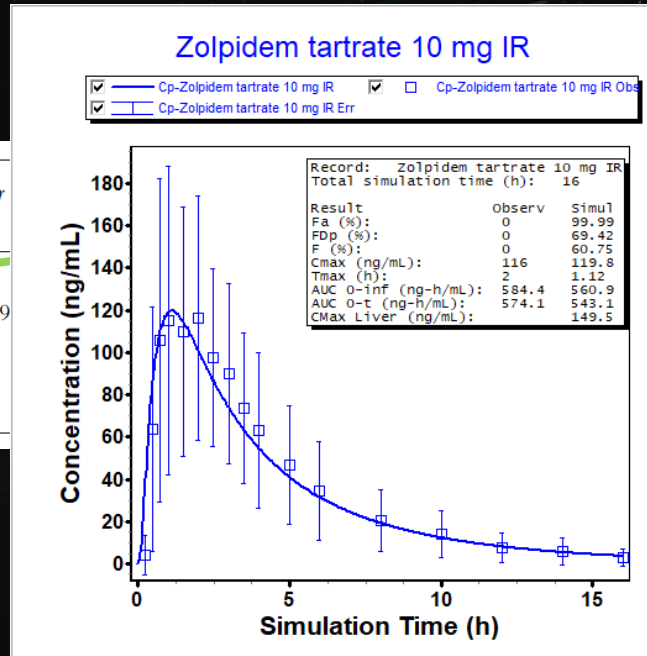
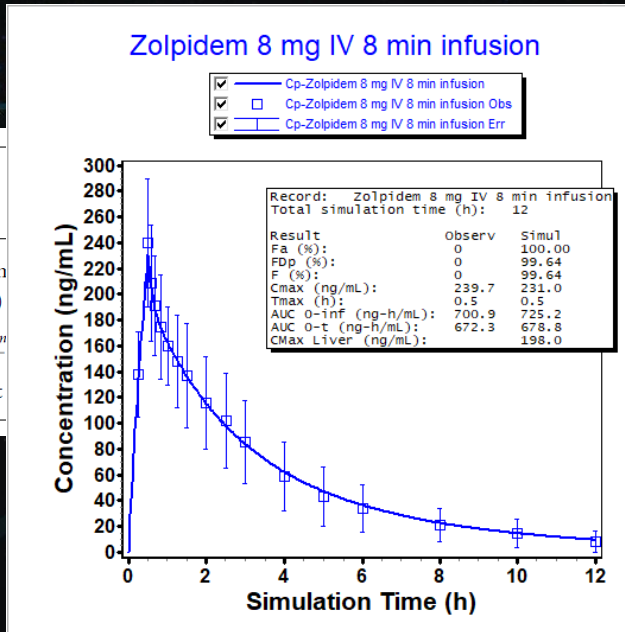
Duodenal solubility at bile salt concentration 2.8mM will be 0.648 mg/mL

Diffusion Layer Thickness
☒ Adjust with changing radius up to maximum
☐ Use constant value
Maximum Diff Layer Thick [um]: 30

OK
Cancel

Disposition parameters

- Use of IV data for distribution + elimination
- Use of in vitro metabolism + scaling for elimination



Factors

Convert T1/2

Transporters

1.35 nmol/min/mg protein

114 μmol/L

0.47309 mg/s Metabolite:

30.925 mg/L

with PBPK location, Vmax will be converted to 3 mg/s/mg-enzyme upon export.

Transfer 3A4 Km and Vmax into Enzyme table

pmol/mg microsomal protein 111 Mwt 57299

Physiology

able. The Km and Vmax values will

Close

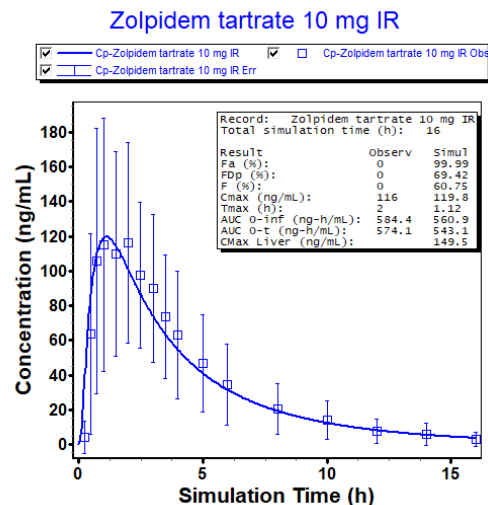
Model validation on oral IR products

Table III. Pharmacokinetic parameters for different doses of zolpidem in healthy volunteers^[25]

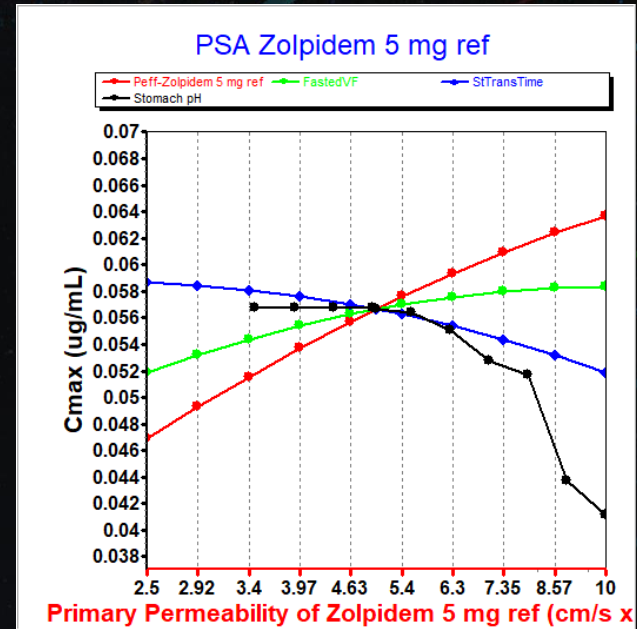
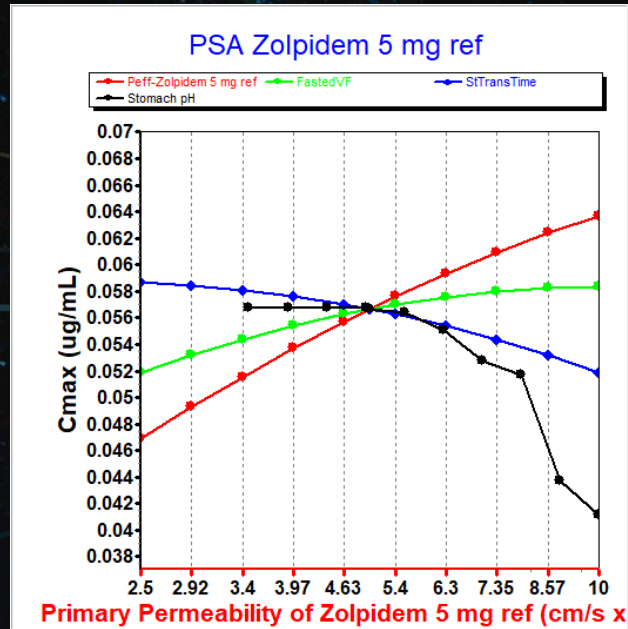
Parameter	Zolpidem dose				
	2.5mg	5mg	10mg	20mg	40mg
AUC_{12h} (μg/L • h)	131.38	259.75	513.87	1004.17	1971.53
Ratio	1.0	0.979	0.978	0.975	0.945
Lower limit of 95% CI		0.907	0.909	0.904	0.867
Upper limit of 95% CI		1.057	1.054	1.053	1.036
AUC_∞ (μg/L • h)	144.27	281.56	551.49	1100.43	2158.58
Ratio	1.0	0.966	0.956	0.973	0.940
Lower limit of 95% CI		0.890	0.880	0.902	0.860
Upper limit of 95% CI		1.054	1.046	1.055	1.039
C_{max} (μg/L)	29.96	58.57	120.82	220.47	388.78
Ratio	1.0	0.972	1.008	0.934	0.817
Lower limit of 95% CI		0.882	0.919	0.835	0.729
Upper limit of 95% CI		1.072	1.106	1.046	0.920

a In the analysis, the 95% confidence intervals (CI) for the ratio between normalised AUC values (AUC value divided by the dose multiplier) and the AUC for the 2.5mg dose showed proportionality for the pharmacokinetic parameters shown in the table, for all doses.

Abbreviations: AUC = area under the plasma concentration-time curve; AUC_{12h} = AUC from zero to 12 hours; AUC_∞ = AUC from zero to infinity; C_{max} = peak plasma concentration.



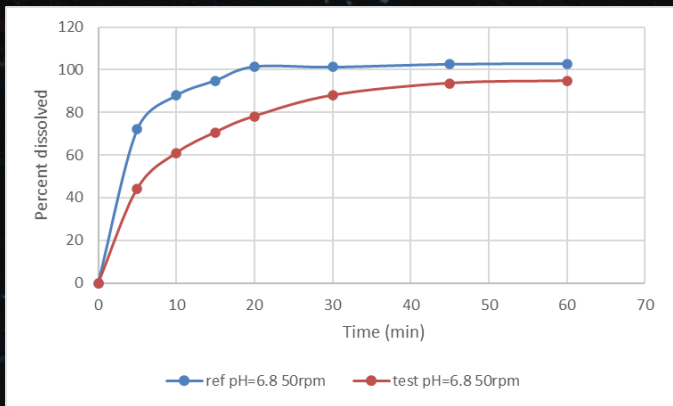
Results of PSA at 5 mg



Percent volume in the small intestine, stomach transit time, stomach pH are the main sources of within subject variability

Model use : prediction of BE

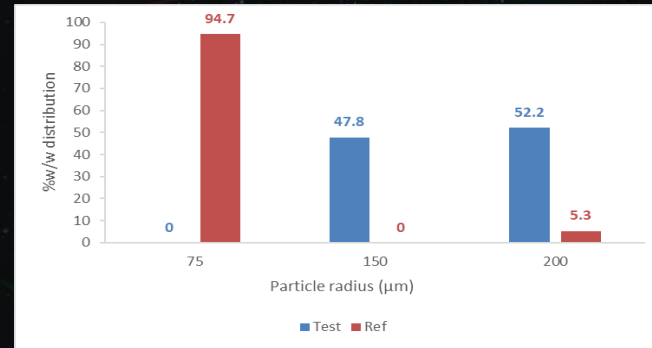
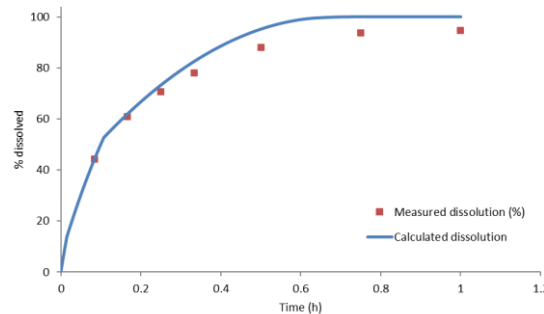
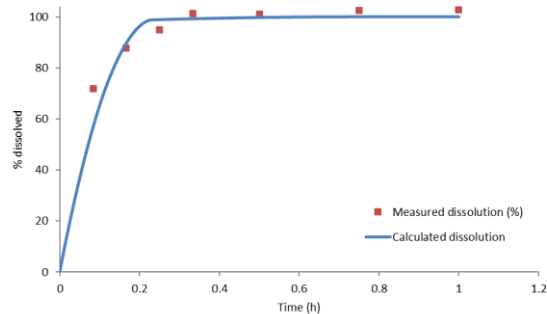
Two 5 mg tablet batches representative of the BE study. Fail f2 comparison at pH 6.8



Use of VBE study to predict bioequivalence

Mechanistic integration of dissolution

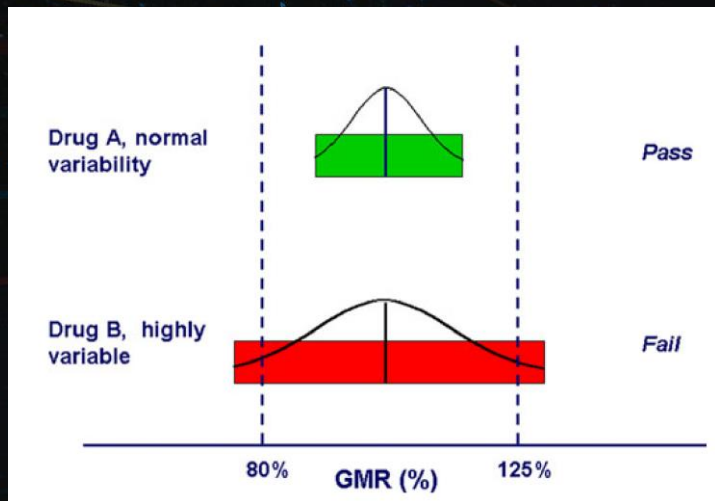
IR products are sensitive to pH, volume, transit time
Use the P-PSD approach to fit the dissolution data ^{A,B,C}
Salt solubility @ pH 6.8 = 2.2 mg/mL



- A: Pepin, X.J.H., et al., Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part I. Mechanistic modelling of drug product dissolution to derive a P-PSD for PBPK model input. *European Journal of Pharmaceutics and Biopharmaceutics*, 2019. 142: p. 421-434. . <https://doi.org/10.1016/j.ejpb.2019.07.014>
- B: Pepin, X., M. Goetschy, and S. Abrahmsén-Alami, Mechanistic models for USP2 dissolution apparatus, including fluid hydrodynamics and sedimentation. *Journal of Pharmaceutical Sciences*, 2021. <https://doi.org/10.1016/j.xphs.2021.10.006>
- C: Pepin, X.J.H., et al., Physiologically Based Biopharmaceutics Model for Selumetinib Food Effect Investigation and Capsule Dissolution Safe Space – Part I: Adults. *Pharmaceutical Research*, 2022. <https://doi.org/10.1007/s11095-022-03339-2>

VBE : Need to power the study to demonstrate BE

Within subject
variability of 30%



Within-subject %CV	GMR (%)	Sample size for a two-way crossover study
15	100	10
	105	12
	110	20
30	100	32
	105	38
	110	68
45	100	66
	105	80
	110	142
60	100	108
	105	132
	110	236
75	100	156
	105	190
	110	340

Davit, B., et al., Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. The AAPS Journal, 2012. 14(4): p. 915-924. <http://dx.doi.org/10.1208/s12248-012-9406-x>

VBE : Virtual BE testing

Population Simulator

File

Parameters

Clear All

Add All

Add Select

Set Defaults

Population

Set PEAR

Load Previous

Create New

Select Outputs

Previous Pop run:
Zolpidem 5 mg
ref-255subjects.stc

GastroPlus(TM)
v.9.8.2000
Population
Simulator File
8/23/2022
1:49:46 PM

Drug Name/ID =
Zolpidem 5 mg ref
25 subjects

Parameter	Lower Limit	Mean Value	Upper Limit	CV%	Distribution
Dose of Zolpidem 5 mg Test (mg)	7.3577	8.04	8.7855	3	Log-Normal
Activity of 3a4 in Duod	5.55E-4	0.0019	0.0063	50	Log-Normal
Primary Permeability of Zolpidem 5	1.1131	5	22.461	65	Log-Normal
Particle Shape Factor of form 1 Of 2	0.7513	1	1.331	10	Log-Normal
Precipitation Particle Radius of Zol	0.7513	1	1.331	10	Log-Normal
Precipitation Time of Zolpidem 5 mg	7513.1	10000	13310	10	Log-Normal
Reference Solubility of Zolpidem 5	0.0601	0.08	0.1065	10	Log-Normal
Fraction Unbound in Enterocytes o	0.7513	1	1	10	Log-Normal
Oral Transit Time of Zolpidem 5 mg	0.1878	0.25	0.3328	10	Log-Normal
Oral Cavity ASF Zolpidem 5 mg Test	0.7513	1	1.331	10	Log-Normal
Duodenum ASF Zolpidem 5 mg Test	2.0631	2.7459	3.6548	10	Log-Normal
Jejunum 1 ASF Zolpidem 5 mg Test	2.0363	2.7103	3.6075	10	Log-Normal
Jejunum 2 ASF Zolpidem 5 mg Test	2.0319	2.7044	3.5996	10	Log-Normal
Ileum 1 ASF Zolpidem 5 mg Test	2.0117	2.6775	3.5638	10	Log-Normal
Ileum 2 ASF Zolpidem 5 mg Test	1.9852	2.6423	3.5169	10	Log-Normal
Ileum 3 ASF Zolpidem 5 mg Test	1.9435	2.5868	3.443	10	Log-Normal
Caecum ASF Zolpidem 5 mg Test	0.7732	1.0291	1.3697	10	Log-Normal
Asc Colon ASF Zolpidem 5 mg Test	1.9121	2.545	3.3874	10	Log-Normal
OralMucosaVolume (mL)	2.6296	3.5	4.6585	10	Log-Normal
SalivaProductionRate (mL/min)	0.7513	1	1.331	10	Log-Normal
Fraction of colon fluid volume in fas	5.6869	10	17.584	20.7	Log-Normal
Fraction of SI fluid volume in fasted	22.748	40	70.337	20.7	Log-Normal
Small Intestine Length (cm)	186.35	310.09	515.99	18.5	Log-Normal
Caecum Length (cm)	6.988	13.323	25.403	24	Log-Normal
Colon Length (cm)	14.655	27.942	53.275	24	Log-Normal

Dose is defined in:

☒ mg ☐ mg/kg ☐ mg/m²

☐ Use this run as reference in BE calculations

Output Points 300

Repeated Trials 1

Sample Size (Maximum = 2500) 25

Intrasubject Settings

☐ No Intrasubject Variability

☒ Simulate Physiologic Intrasubject Variability

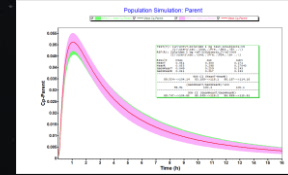
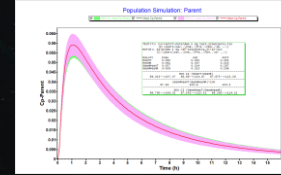
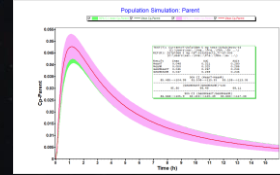
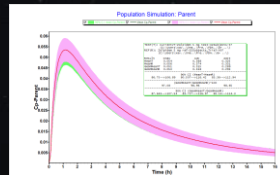
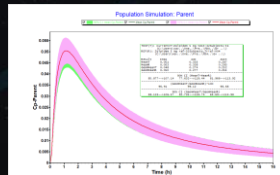
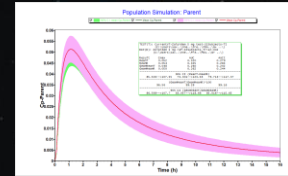
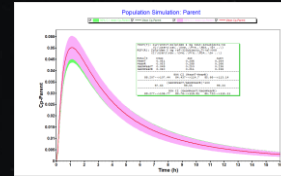
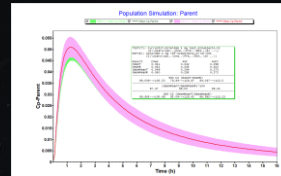
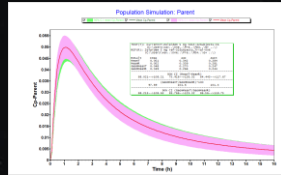
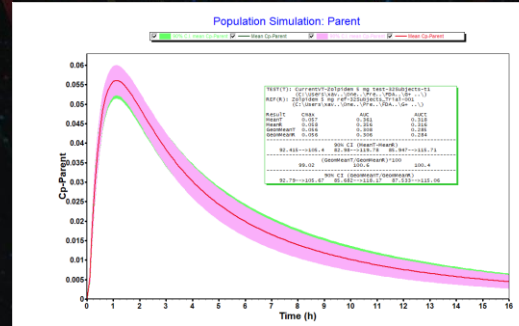
☐ Apply Intrasubject CV% to Cmax and AUC

Cmax AUC

Sampling Distribution

CV % 10 10

OK Cancel



Take home message

- Plug and Play and GastroPlus are powerful tools.
- The impact of formulation's dissolution on its absorption can be evaluated via mechanistic modeling of absorption and allow to limit the number of clinical trials during the formulation design process.
- Plug and Play will enhance your R&D program.

 *SimulationsPlus*

MIDD 

Model Informed Drug Development + 2023

Q&A

Questions & Answers