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.

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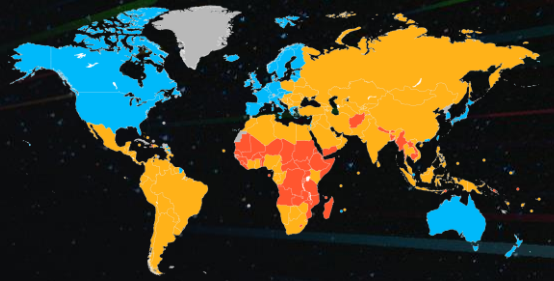
Harnessing the Power of Emerging Markets: A Pharmaceutical Industry Opportunity

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.

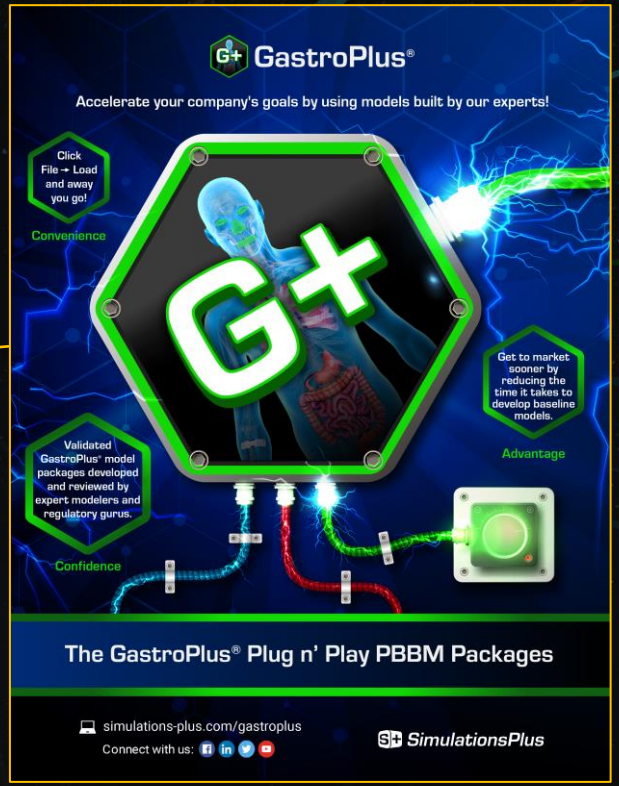
Affordability and Cost-Effective : Generics are more affordable and accessible to a wider range of patients.

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



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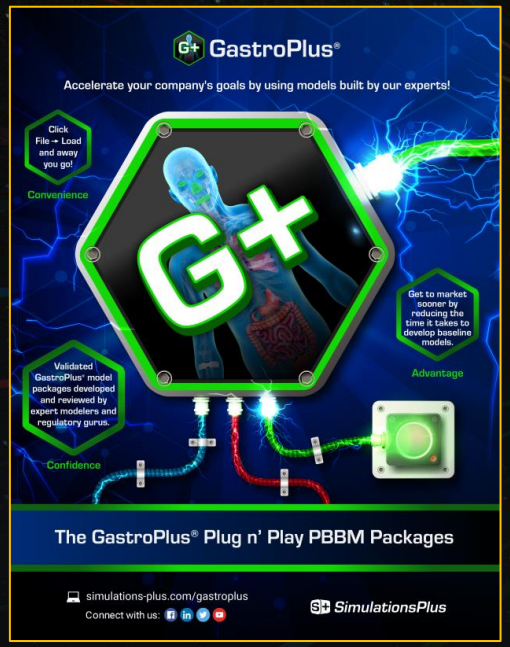
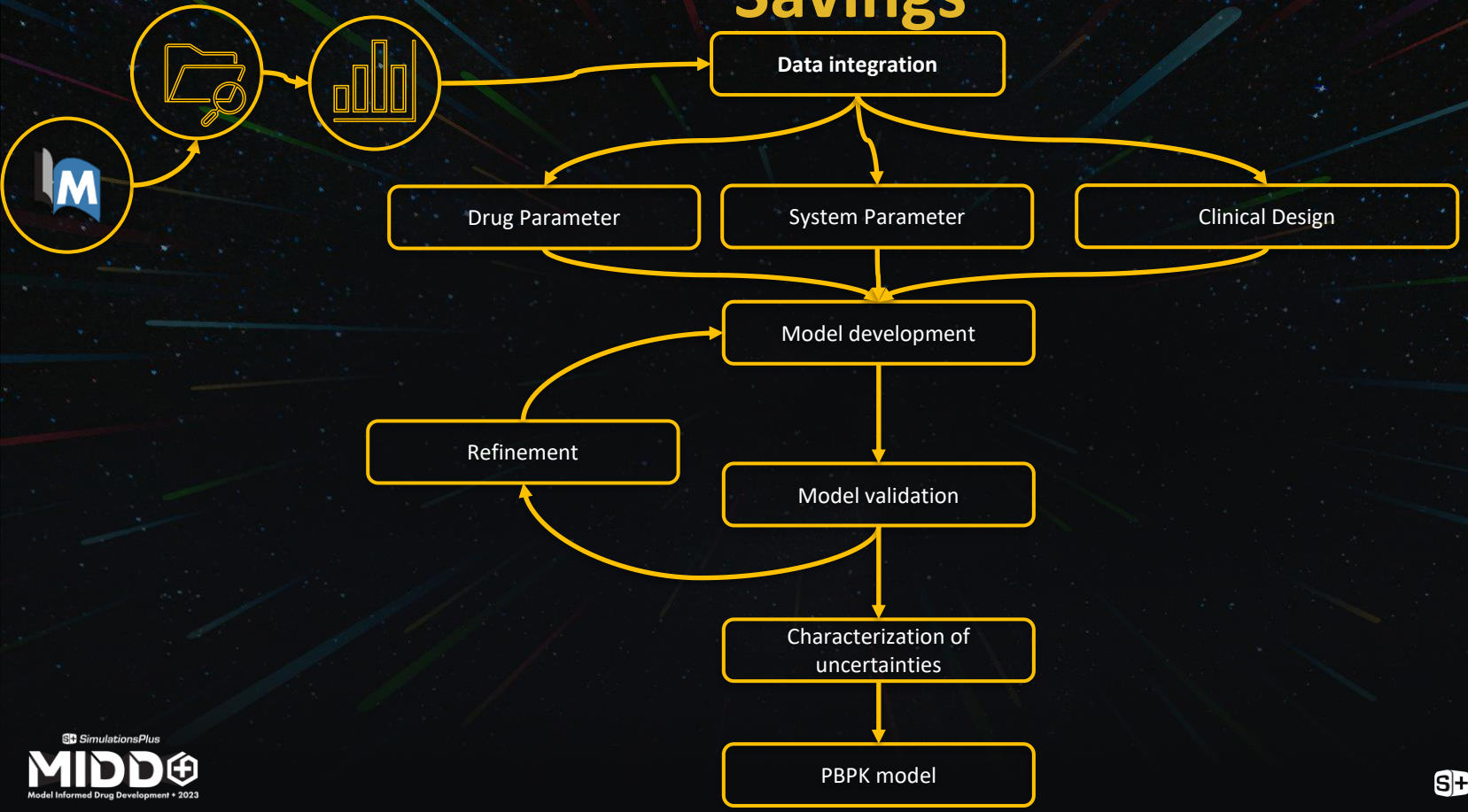
Simplify the Generic Drug Product Development Process



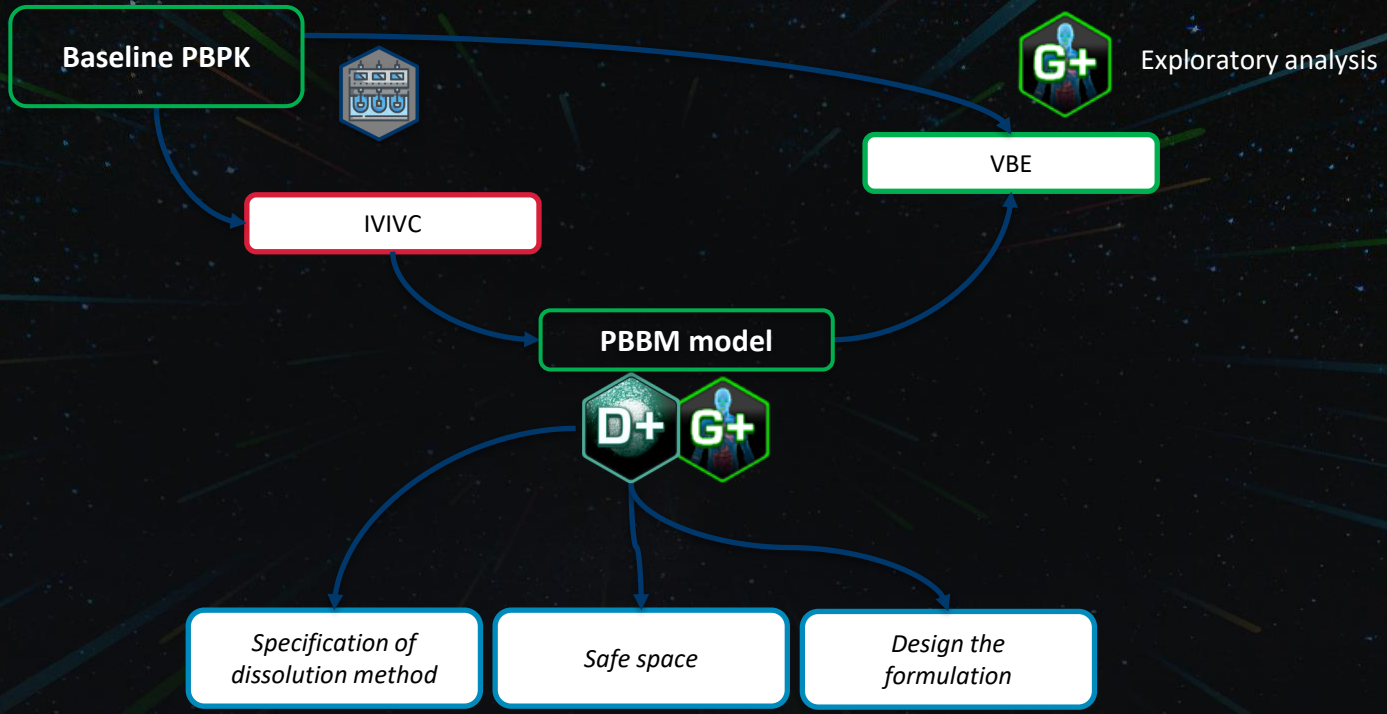
Three tiers of PBBM models

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

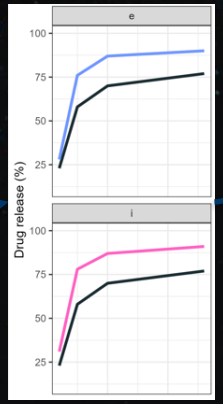
Achieving Success through Quality and Time Savings



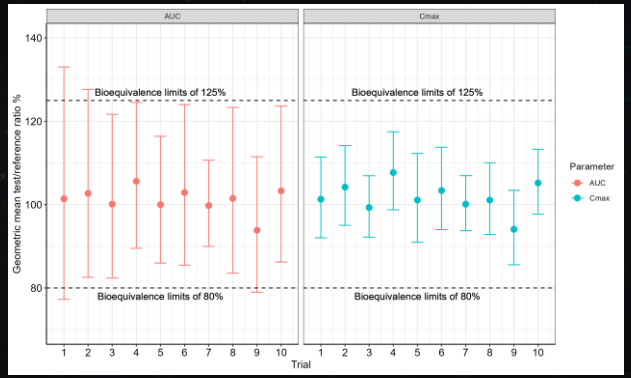
Achieving Success through Quality and Time Savings



How does Plug and Play work



vBE



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What are the benefits of using Plug and Play?

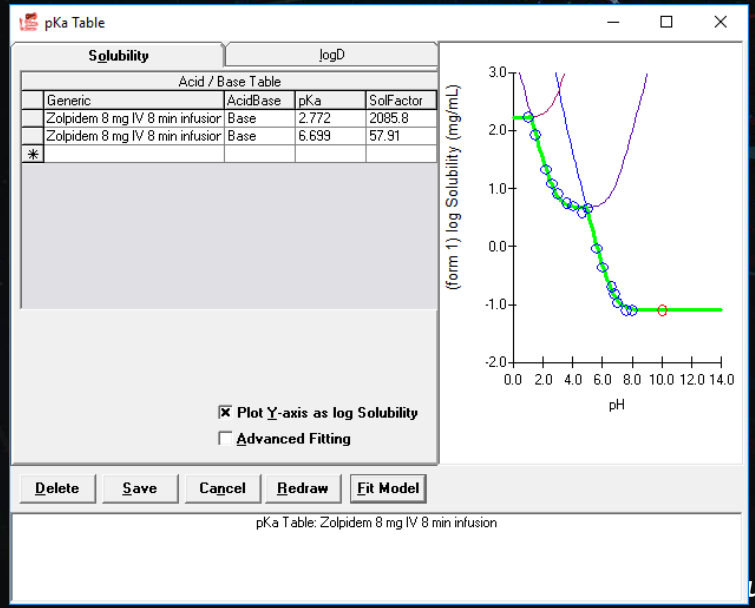
- Transform your analysis into a high-performance operation and reduce analysis time while increasing result accuracy.
- Reduce time and costs with data curation.
- Reduce costs and time with efficient training and professional development.
- Increase the efficiency of your R&D program.
- All models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

Zolpidem ODT

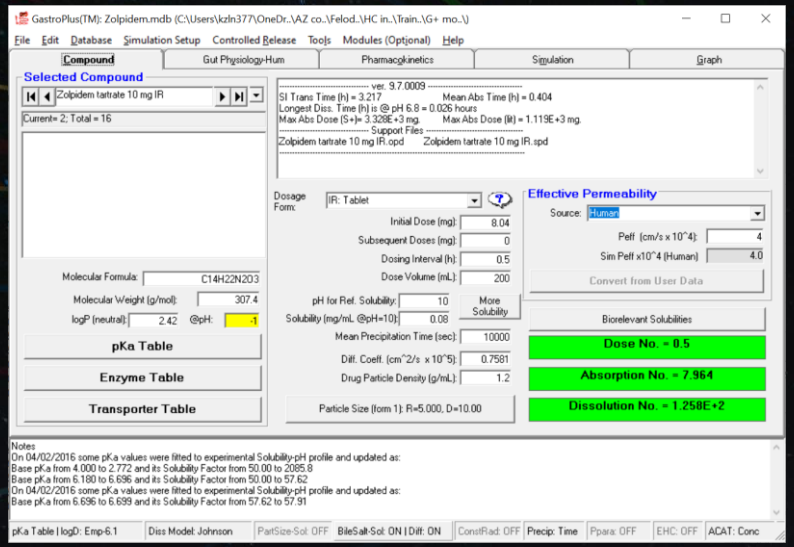
Objective : Predict likelihood of clinical trial outcome (BE between test and reference product)

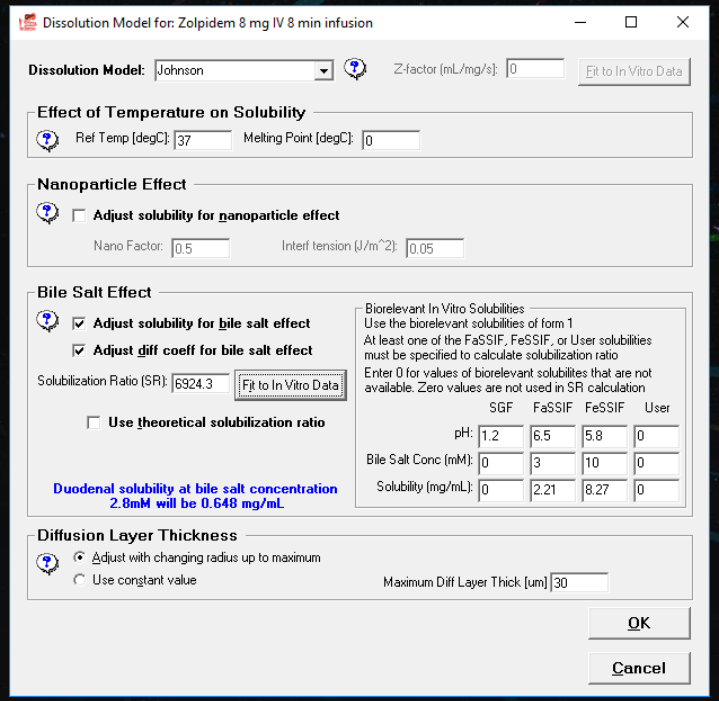
Zolpidem hemitartrate– Physico-chemical and biopharmaceutical properties

- MW = 764.88 $g.mol^{-1}$ (=307.4 for active moiety)
- Salt to base ratio = 1.24
- Caco2 scaled to human jejunal Peff = 4 $x10^{-4}$cm/s
- fu,p = 7.5%, B:P = 0.76
- Log P= 2.42
- Weak base
  - pKa = 6.18
- Aqueous solubility
  - pH dependent
  - S_0 = 0.08 mg/mL @ pH 10



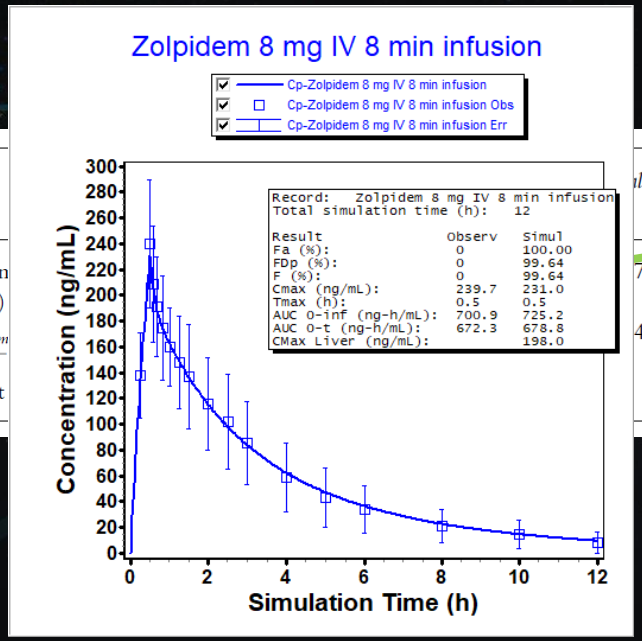
Zolpidem hemitartrate– Physico-chemical and biopharmaceutical properties

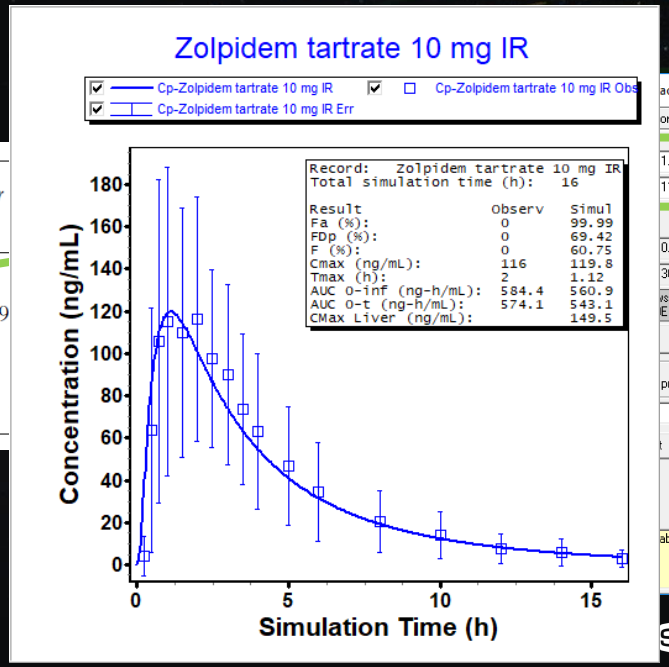


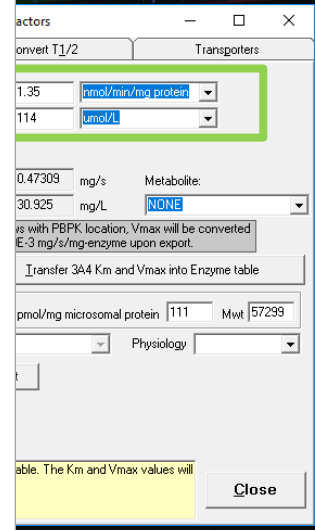


Disposition parameters

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







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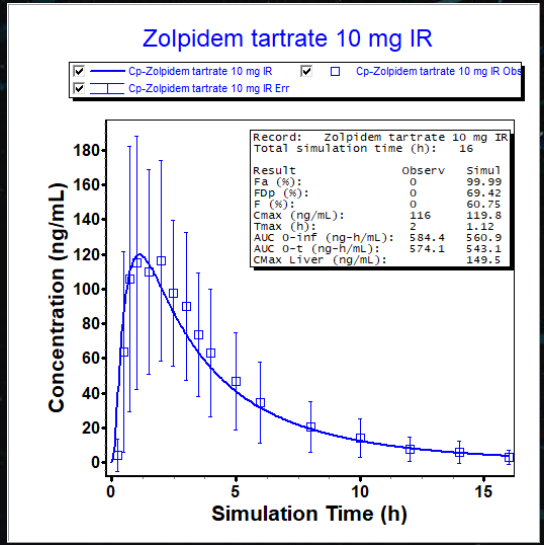
Model validation on oral IR products

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

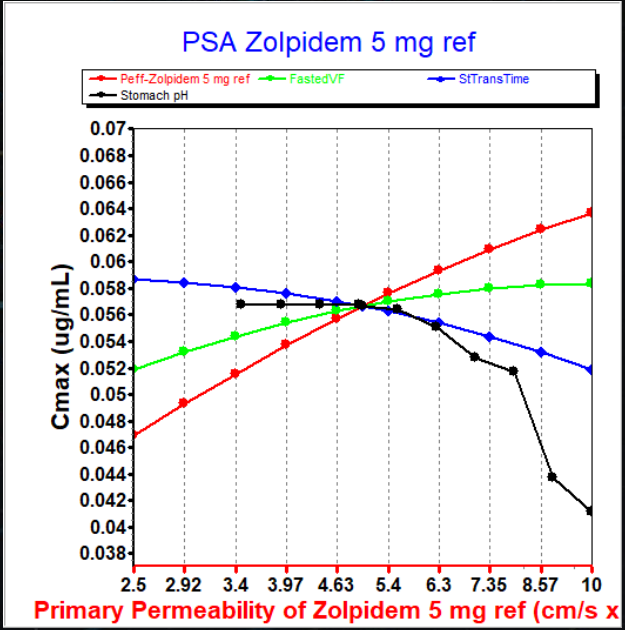
Parameter	Zolpidem dose				
	2.5mg	5mg	10mg	20mg	40mg
AUC_{12h} (µg/L • h)	**131.38**	**259.75**	**513.87**	**1004.17**	**1971.53**
Ratio	1.0	0.979	0.978	0.975	0.945
Lower limit of 95% CI		0.907	0.909	0.904	0.867
Upper limit of 95% CI		1.057	1.054	1.053	1.036
AUC_{∞} (µg/L • h)	**144.27**	**281.56**	**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

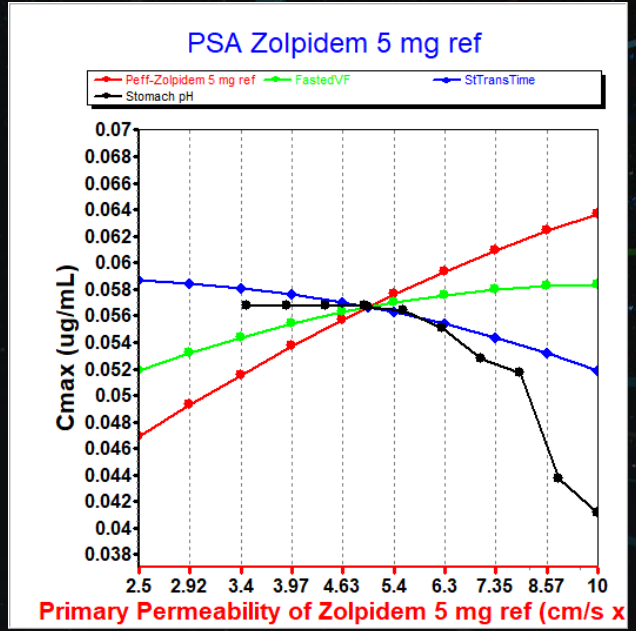
a In the analysis, the 95% confidence intervals (CI) for the ratio between normalised AUC values (AUC value divided by the dose multiplier) and the AUC for the 2.5mg dose showed proportionality for the pharmacokinetic parameters shown in the table, for all doses.

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

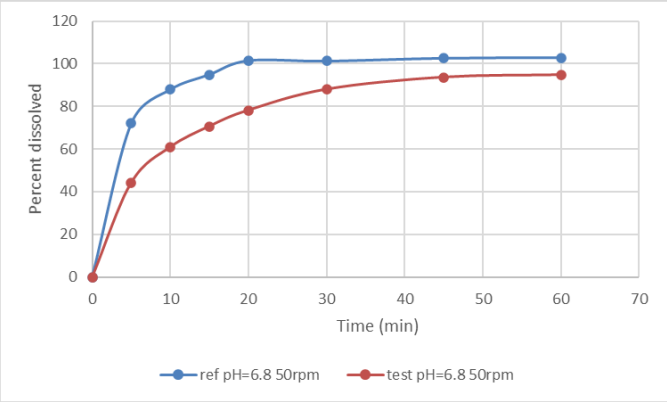




Percent volume in the small intestine, stomach transit time, stomach pH are the main sources of within subject variability

Model use : prediction of BE

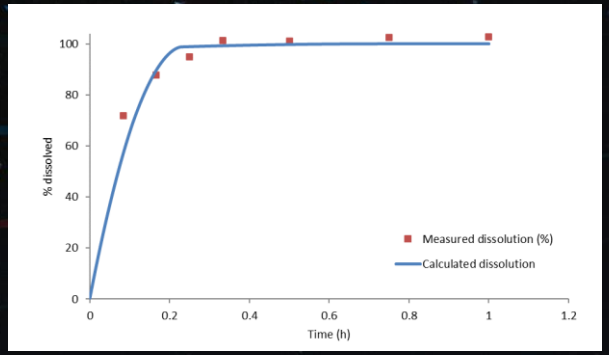
Two 5 mg tablet batches representative of the BE study. Fail f2 comparison at pH 6.8

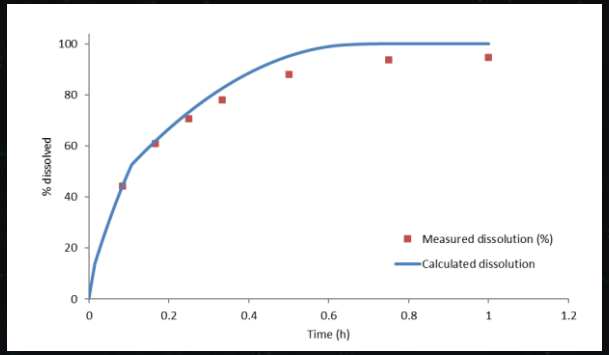


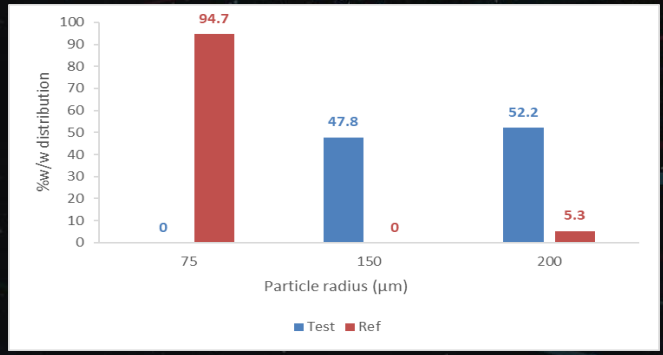
Use of VBE study to predict bioequivalence

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



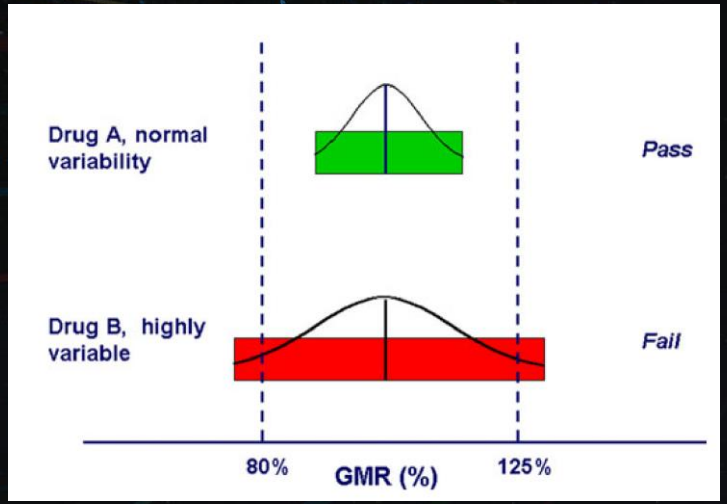




A: Pepin, X.J.H., et al., Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part I. Mechanistic modelling of drug product dissolution to derive a P-PSD for PBPK model input. European Journal of Pharmaceutics and Biopharmaceutics, 2019. 142: p. 421-434. . https://doi.org/10.1016/j.ejpb.2019.07.014
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

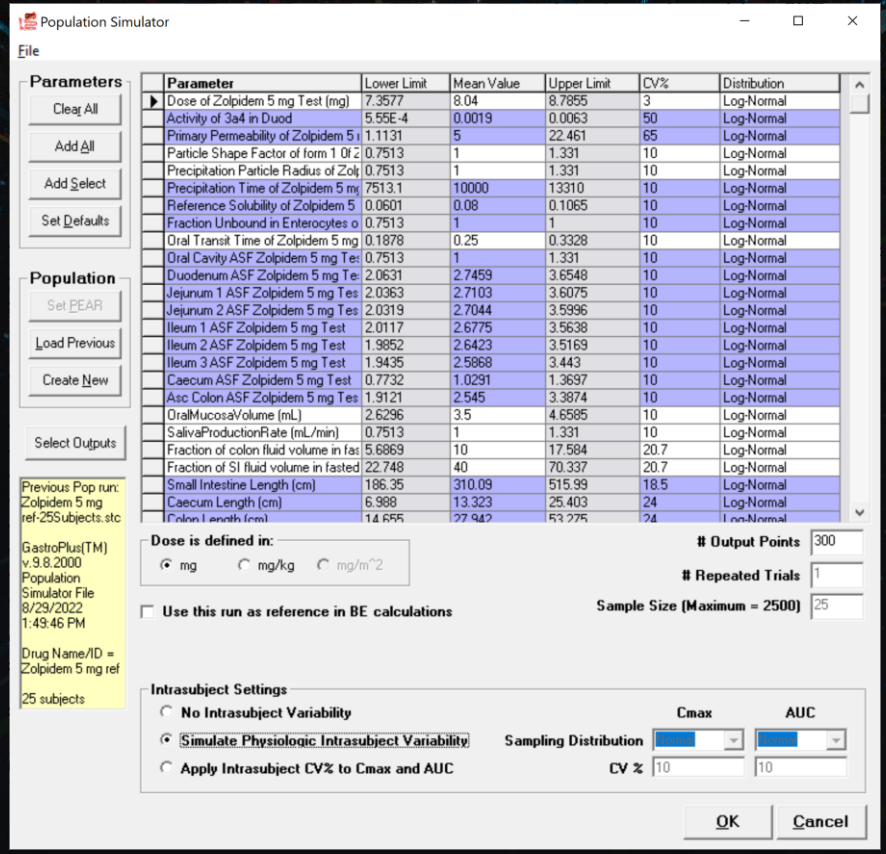
Within subject variability of 30%



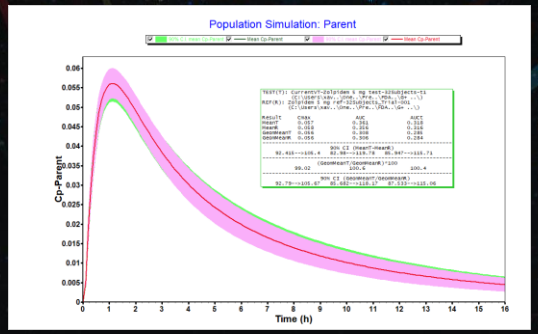
Within-subject %CV	GMR (%)	Sample size for a two-way crossover study
15	100	10
	105	12
	110	20
30	100	32
	105	38
	110	68
45	100	66
	105	80
	110	142
60	100	108
	105	132
	110	236
75	100	156
	105	190
	110	340

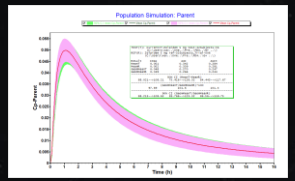
Davit, B., et al., Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. The AAPS Journal, 2012. 14(4): p. 915-924. http://dx.doi.org/10.1208/s12248-012-9406-x

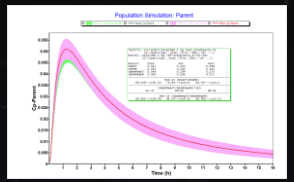
VBE : Virtual BE testing

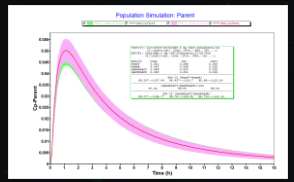


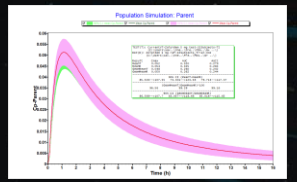
VBE : Test vs Ref : BE predicted

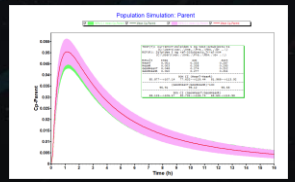


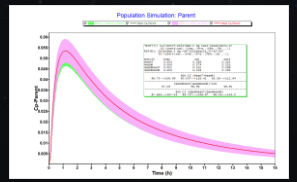


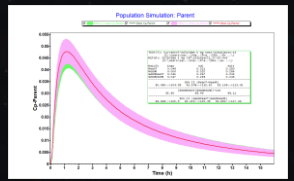


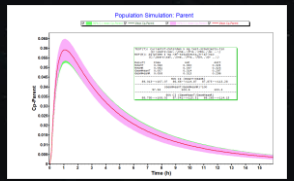


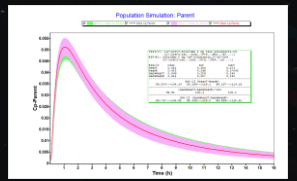












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Take home message

- 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.

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MIDD+

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Q&A

Questions & Answers