

S+ *SimulationsPlus*



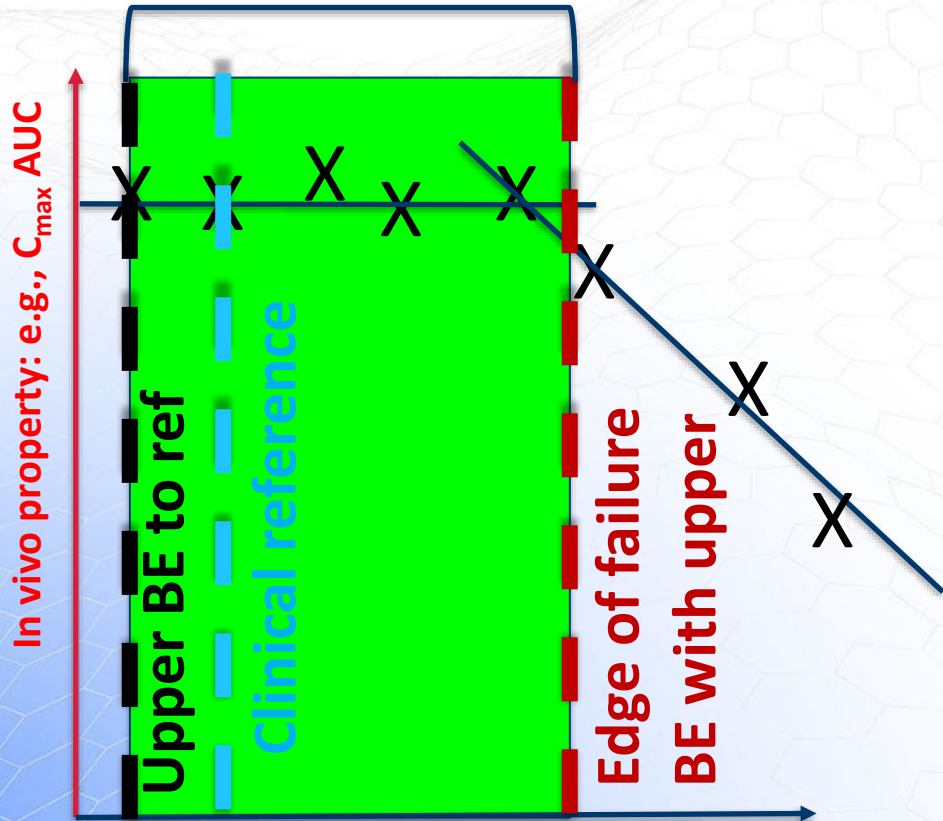
BO Session I : Safe space(s)

M-CERSI workshop
Xavier Pepin

2023 August 30

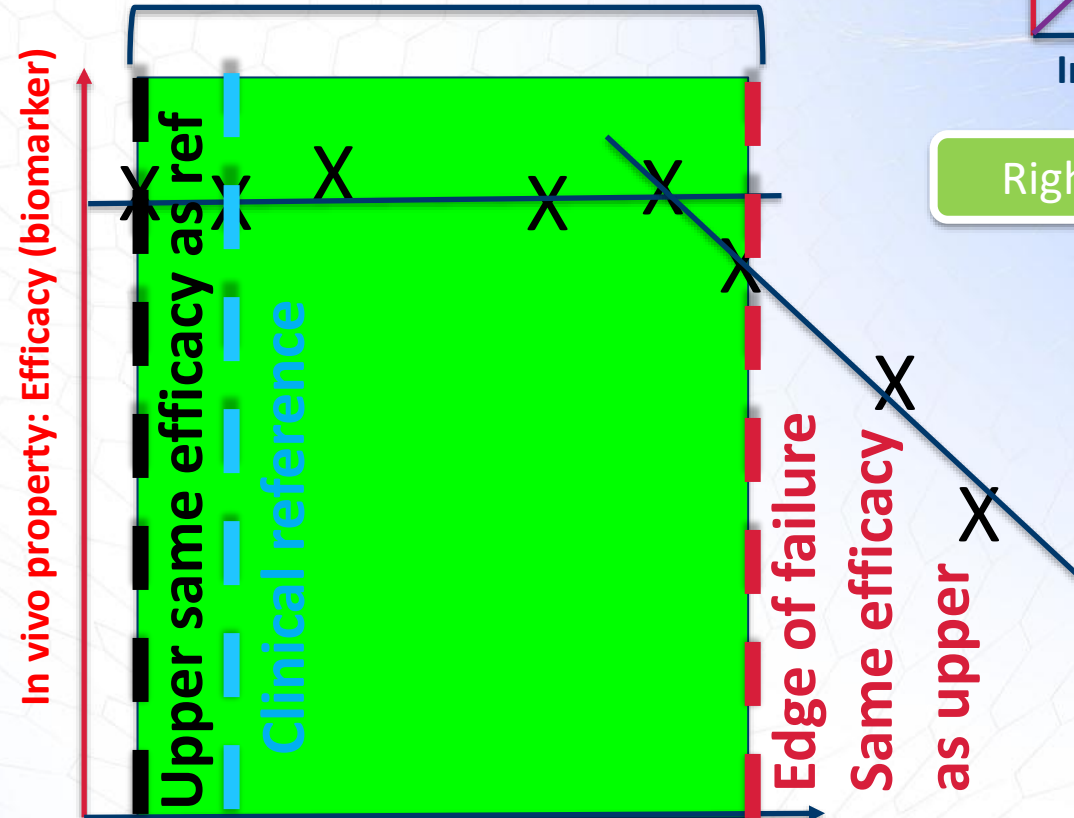
Safe space(s)

Safe space based on BE

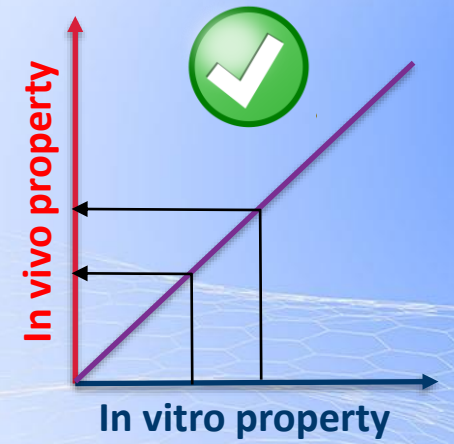


CBA: e.g. Particle size, T80% dissolution, compression force

Safe space based on PK-PD



CBA: e.g. Particle size, T80% dissolution, compression force



Right discrimination

Considerations to establish safe spaces

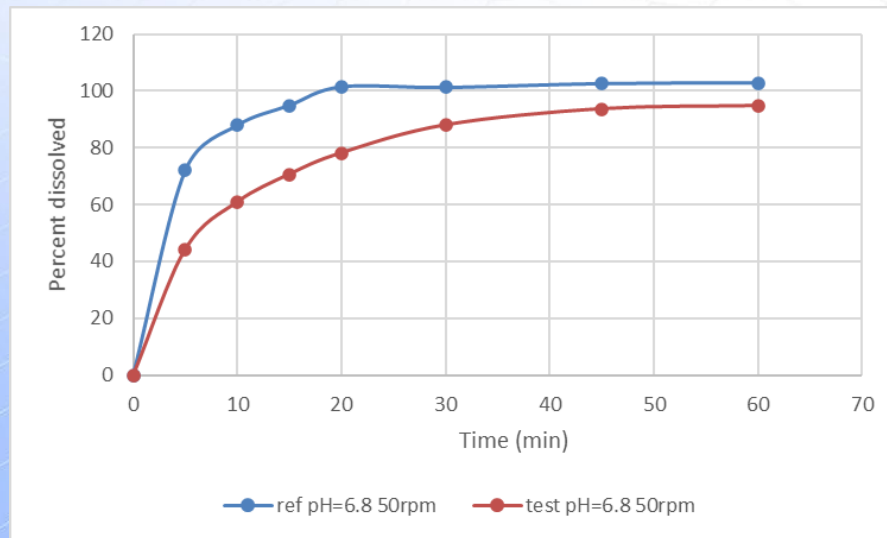
- PBBM BE based safe space
 - Perform sensitivity analyses to determine GMR evolution with CBA
 - Polymorphic impurity, hardness, surface to volume ratio, thickness of coating... All should influence DP dissolution with the biopredictive method
 - Perform 10 VBE studies with the appropriate size (based on IOV)
 - 10/10 VBEs should pass pre-defined BE criteria for both ref vs ref and test vs ref
- PBBM+PKPD based safe space
 - Perform sensitivity analyses to determine GMR evolution with CBA
 - Check size of BE safe space (see above)
 - Predict efficacy across all exposure (Cmax and AUC) using PBBM and PKPD + PKTD
 - Predict the edge of failure based on efficacy and tox
 - Conclude on the safe space

Case studies

- BCS class 1 : Zolpidem : Safe space for dissolution based on VBE
- BCS class 3-4: Acyclovir : Safe space based on extrapolation
- BCS class 2: Acalabrutinib maleate tablet : Safe space for dissolution based on PBBM+PKPD

Case study 1: PBBM prediction of BE for Zolpidem IR tablets

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



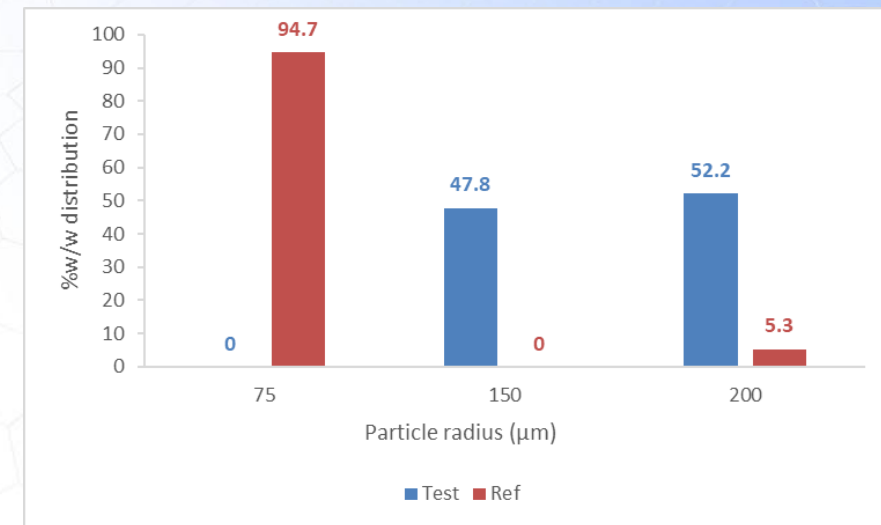
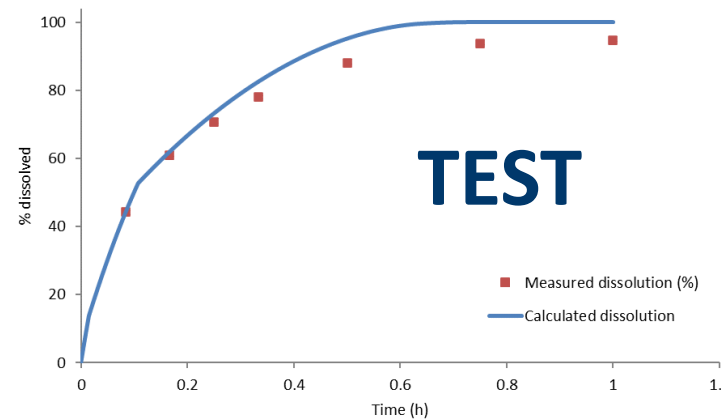
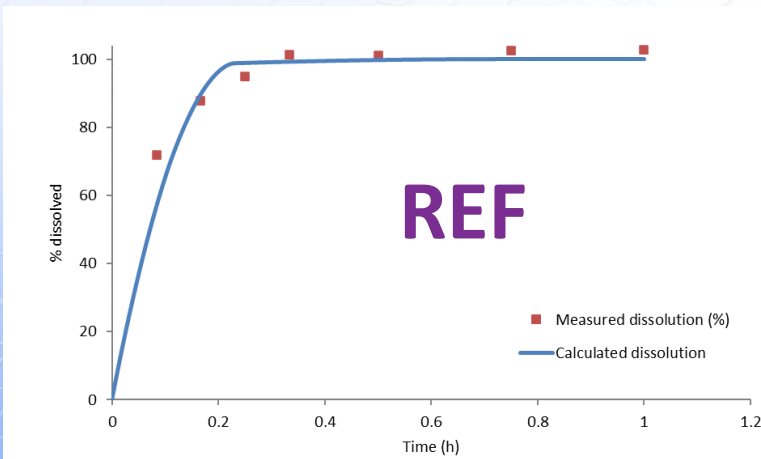
Use of VBE study to predict bioequivalence = same process as for edge of failure determination
Real batches could be virtual batches representative of process capability !

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. Abrahamsén-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 : Virtual BE testing

- N=10 trials of n=25 subjects (default)
- Ref = current 5 mg tablet
- Test = ODT tablet
- Cross over trials with physiological variability
- 1st trial : Ref vs Ref : See if the within subject variability is not too high vs # of subjects per study

The screenshot shows the Population Simulator software interface. The main window displays a table of parameters and their values. The table has columns for Parameter, Lower Limit, Mean Value, Upper Limit, CV%, and Distribution. The parameters listed include various physiological and pharmacokinetic parameters for Zolpidem 5 mg Test, such as Dose, Activity of 3a4 in Duod, Primary Permeability, Particle Shape Factor, Precipitation Particle Radius, Precipitation Time, Reference Solubility, Fraction Unbound, Oral Transit Time, Oral Cavity ASF, Duodenum ASF, Jejunum 1 ASF, Jejunum 2 ASF, Ileum 1 ASF, Ileum 2 ASF, Ileum 3 ASF, Caecum ASF, Asc Colon ASF, Oral Mucosa Volume, Saliva Production Rate, Fraction of colon fluid volume, Fraction of SI fluid volume, Small Intestine Length, Caecum Length, and Colon Length.

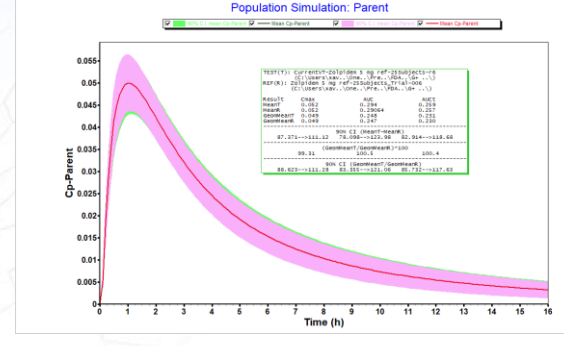
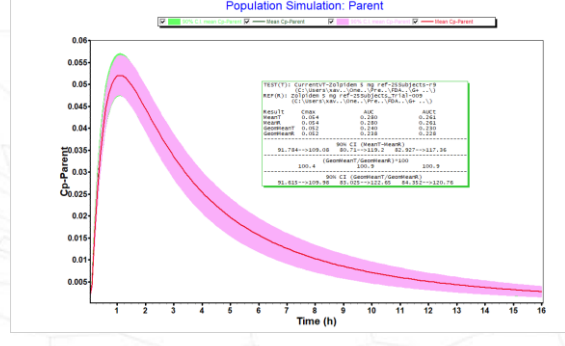
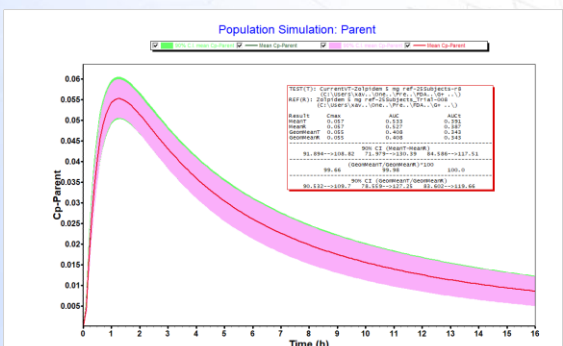
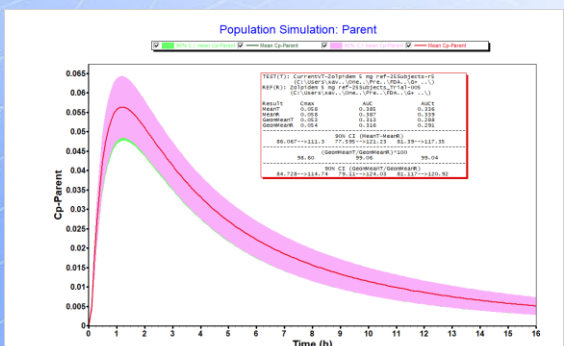
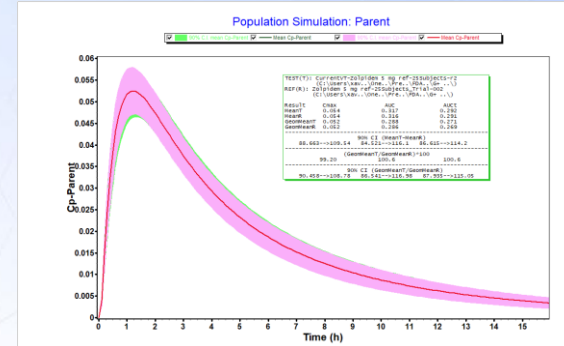
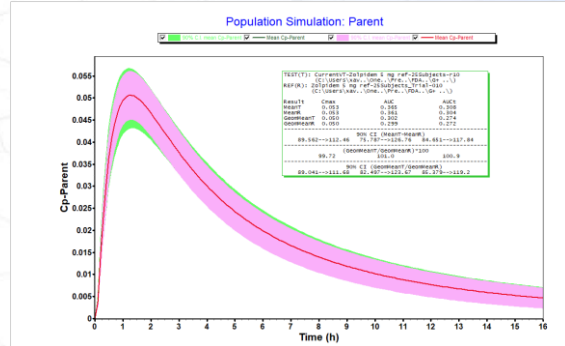
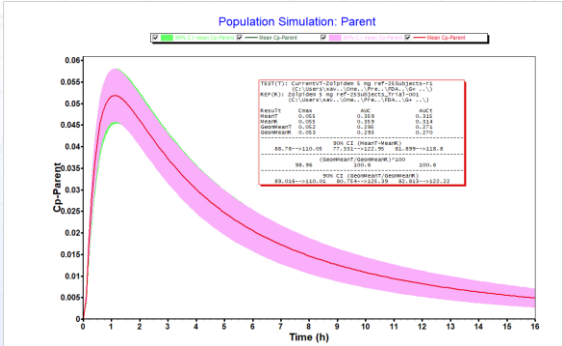
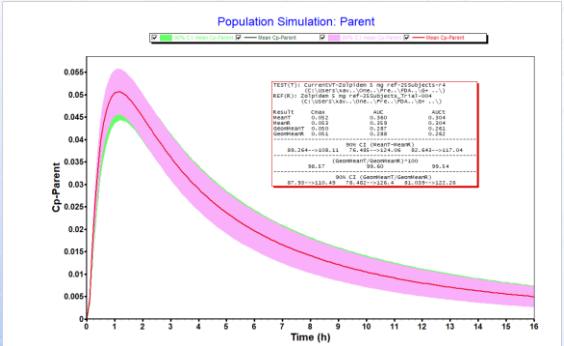
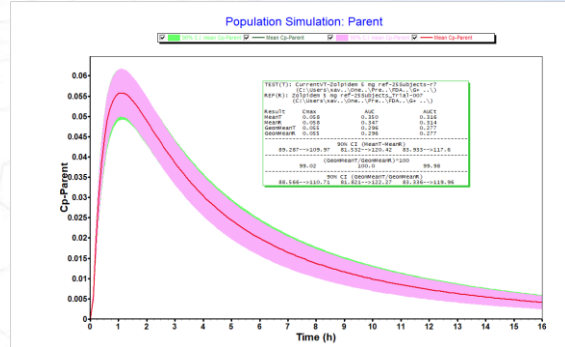
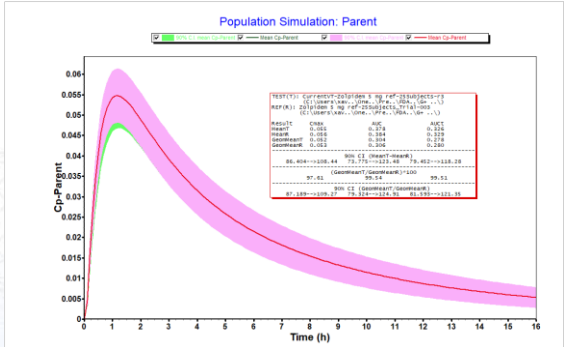
Parameter	Lower Limit	Mean Value	Upper Limit	CV%	Distribution
Dose of Zolpidem 5 mg Test (mg)	7.3577	8.04	8.7855	3	Log-Normal
Activity of 3a4 in Duod	5.55E-4	0.0019	0.0063	50	Log-Normal
Primary Permeability of Zolpidem 5	1.1131	5	22.461	65	Log-Normal
Particle Shape Factor of form 1 Of 2	0.7513	1	1.331	10	Log-Normal
Precipitation Particle Radius of Zolp	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 Te	0.7513	1	1.331	10	Log-Normal
Duodenum ASF Zolpidem 5 mg Te	2.0631	2.7459	3.6548	10	Log-Normal
Jejunum 1 ASF Zolpidem 5 mg Tes	2.0363	2.7103	3.6075	10	Log-Normal
Jejunum 2 ASF Zolpidem 5 mg Tes	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 Tes	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

The interface also includes a 'Parameters' panel on the left with buttons for 'Clear All', 'Add All', 'Add Select', and 'Set Defaults'. Below this is a 'Population' panel with buttons for 'Set PEAR', 'Load Previous', and 'Create New'. A 'Select Outputs' panel is also present. The bottom right section contains simulation settings: 'Dose is defined in:' (mg, mg/kg, mg/m²), '# Output Points' (300), '# Repeated Trials' (1), 'Sample Size (Maximum = 2500)' (25), and 'Intrasubject Settings' (No Intrasubject Variability, Simulate Physiologic Intrasubject Variability, Apply Intrasubject CV% to Cmax and AUC). The 'Simulate Physiologic Intrasubject Variability' option is selected, and 'Sampling Distribution' is set to 'Log-Normal' for both Cmax and AUC, with 'CV %' set to 10. 'OK' and 'Cancel' buttons are at the bottom right.

VBE : Ref vs Ref : failure to demonstrate BE with n=25

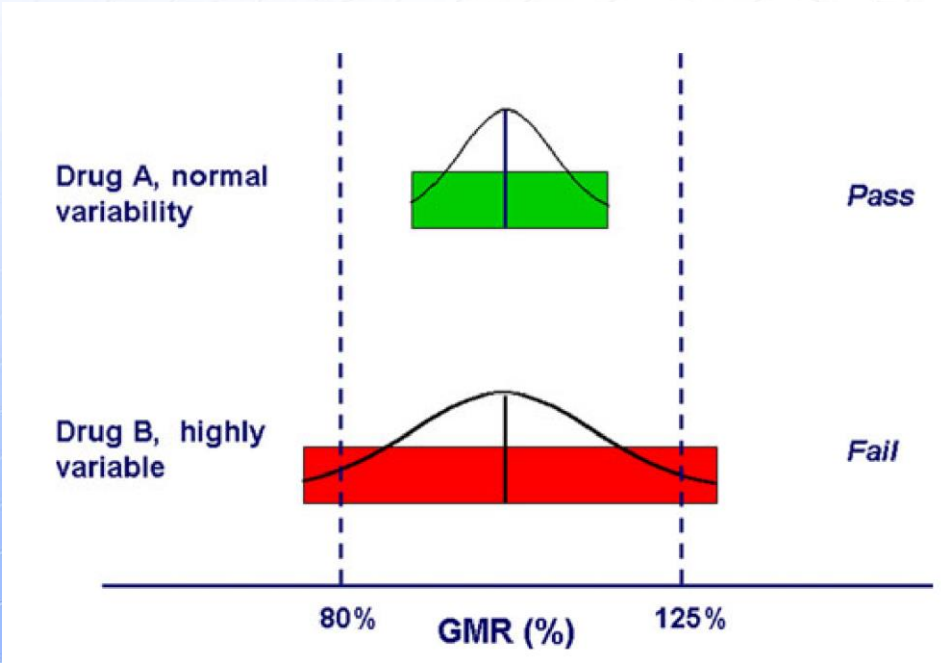
5 studies failed
5 studies passed

Within subject
variability of 30%



VBE : Need to power the study to demonstrate BE

Within subject variability of 30%



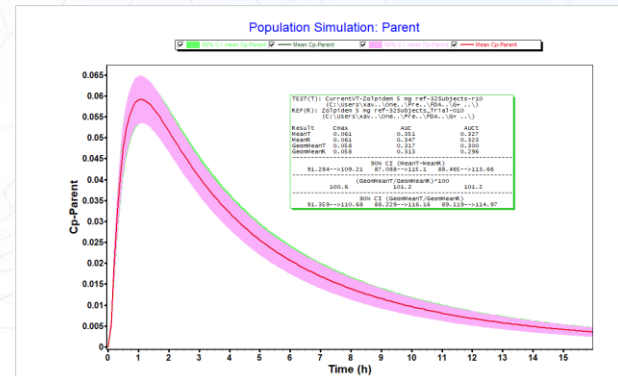
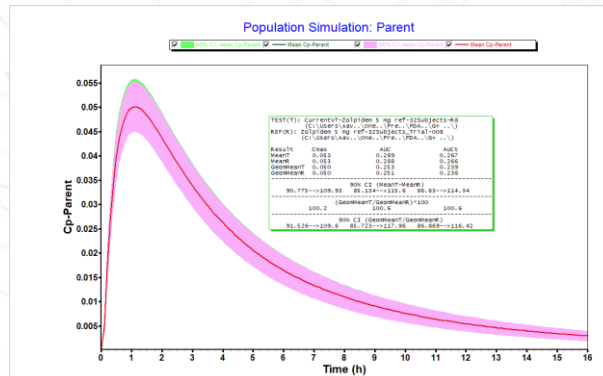
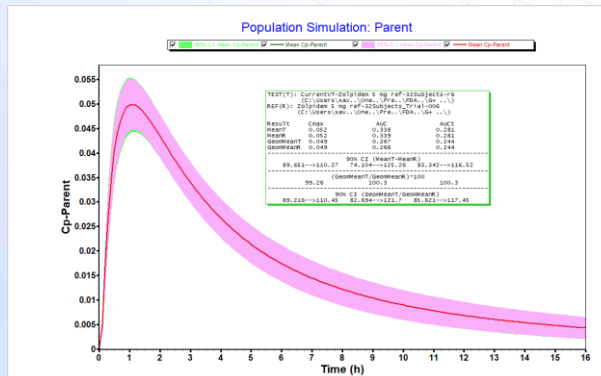
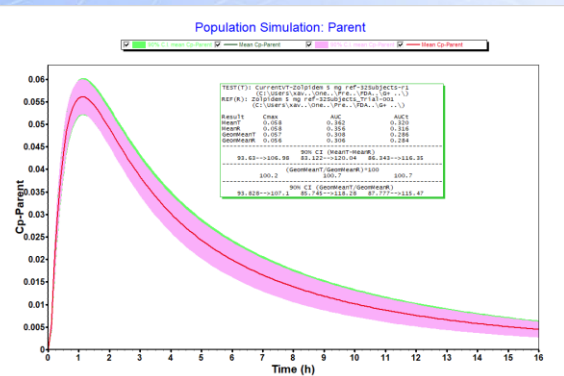
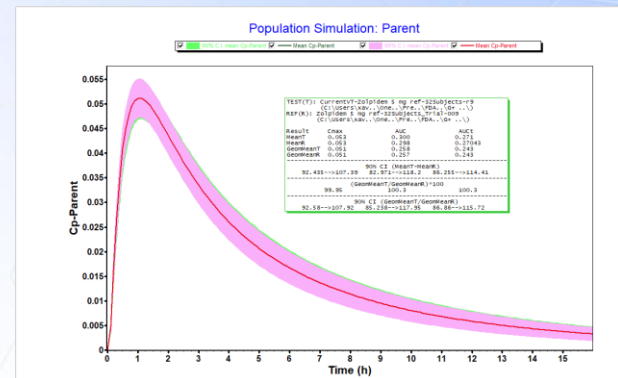
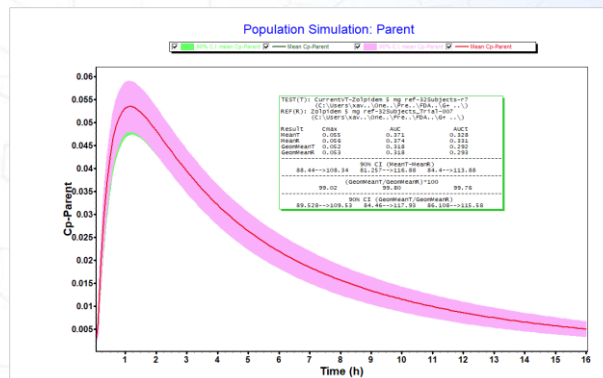
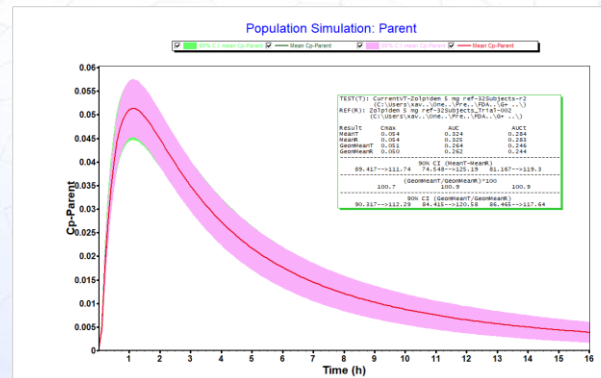
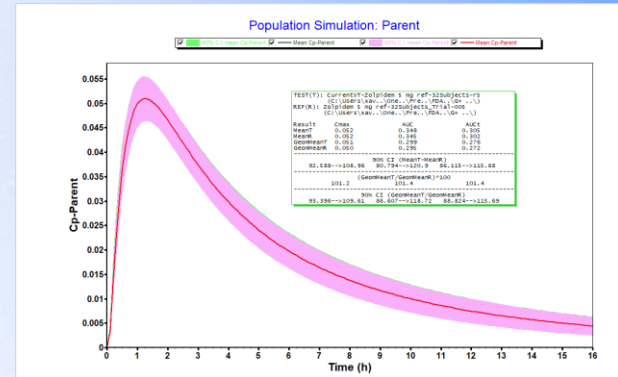
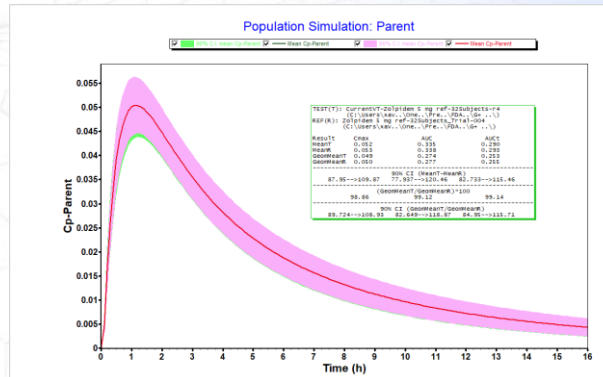
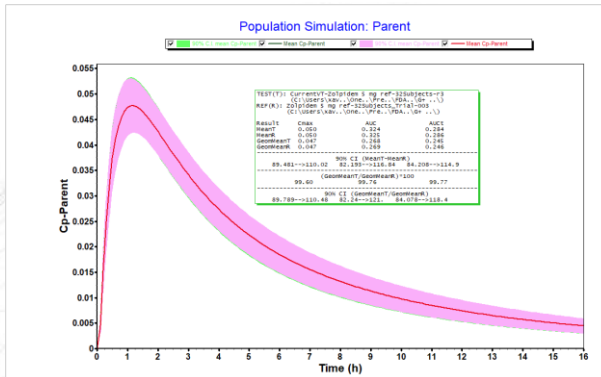
Within-subject %CV	GMR (%)	Sample size for a two-way crossover study
15	100	10
	105	12
	110	20
30	100	32
	105	38
	110	68
45	100	66
	105	80
	110	142
60	100	108
	105	132
	110	236
75	100	156
	105	190
	110	340

Need 32 subjects to demonstrate BE for the same formulation with 30% Within-S %CV

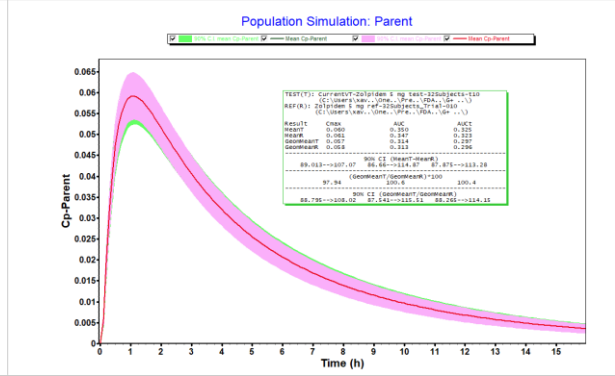
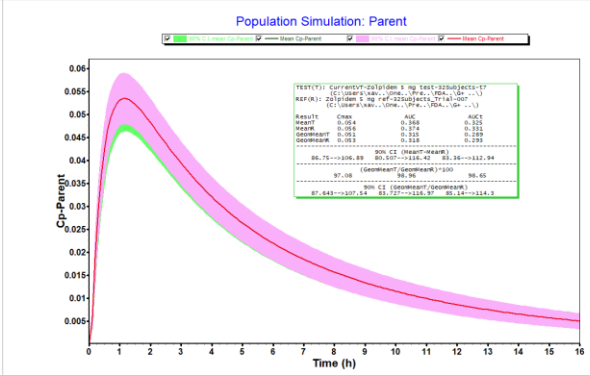
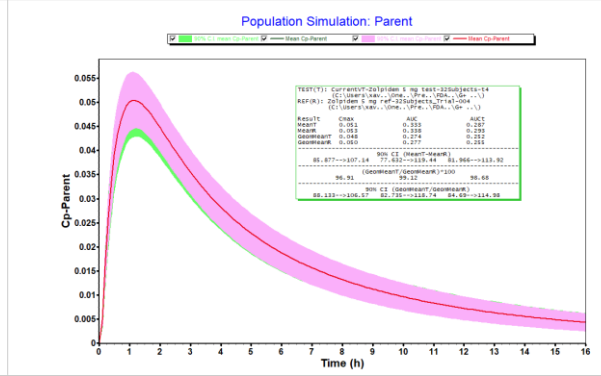
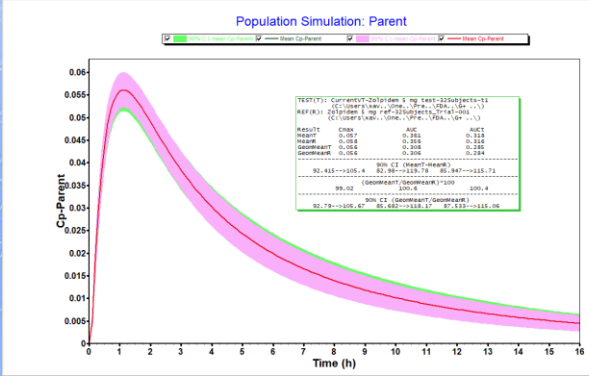
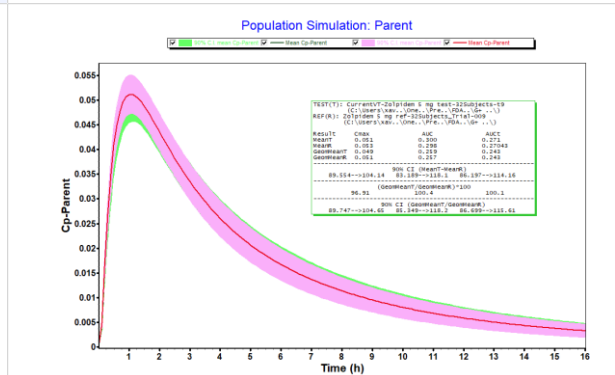
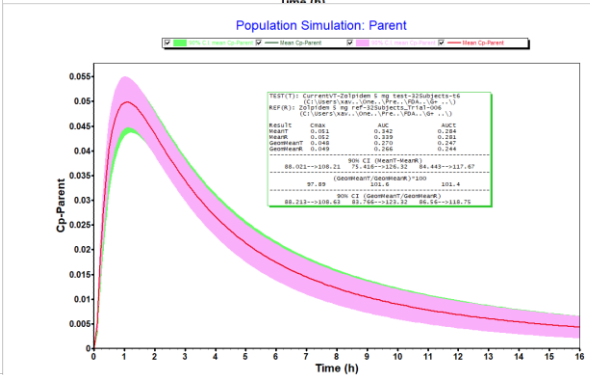
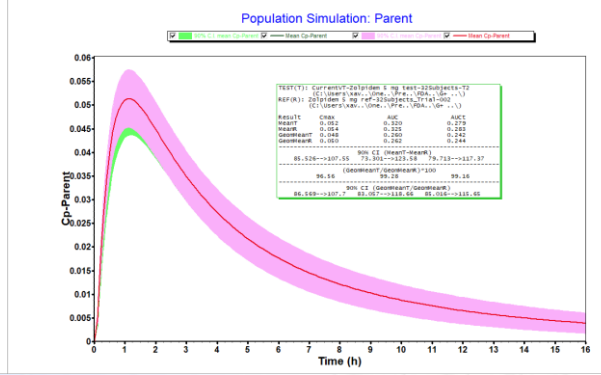
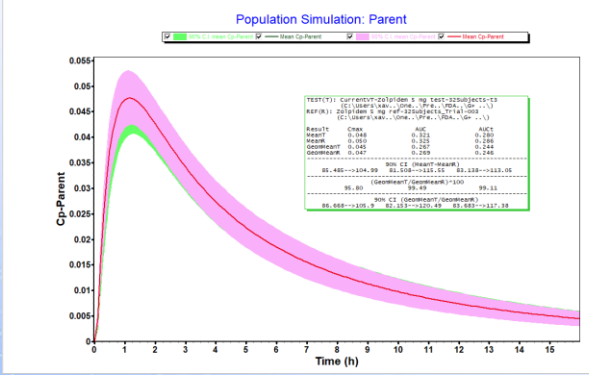
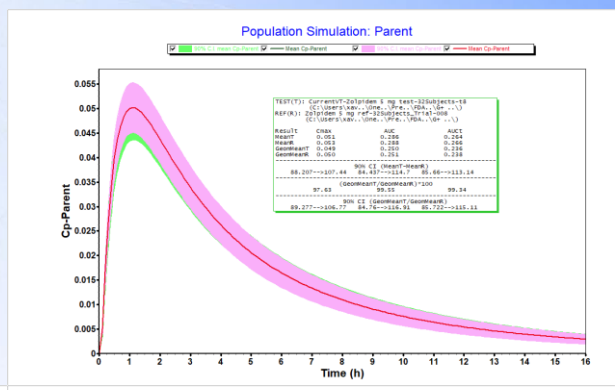
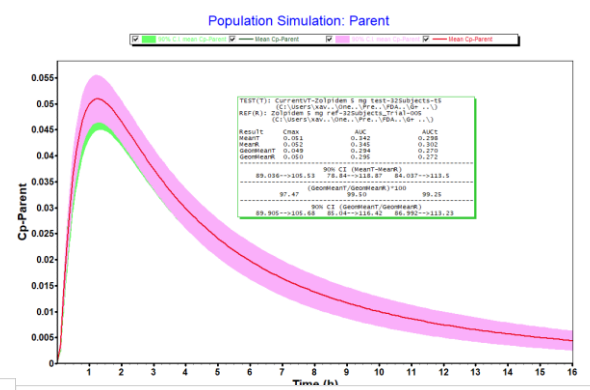
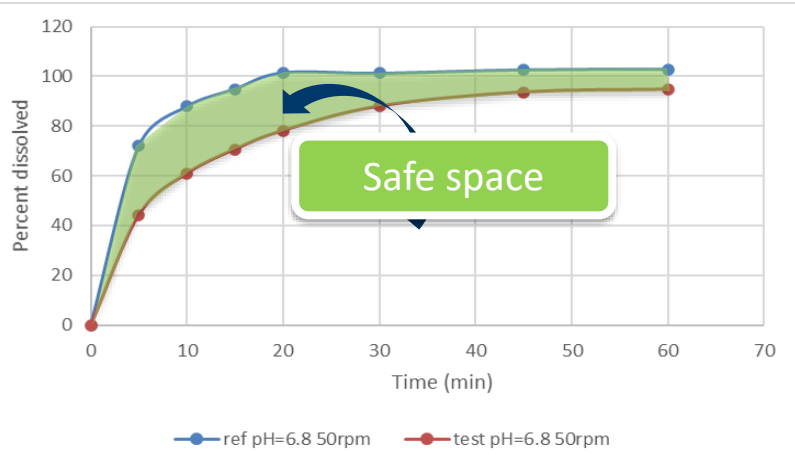
Davit, B., et al., Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. The AAPS Journal, 2012. 14(4): p. 915-924. <http://dx.doi.org/10.1208/s12248-012-9406-x>

VBE : Ref vs Ref : BE with n=32

N=32 subject enough to demonstrate BE with the same formulation

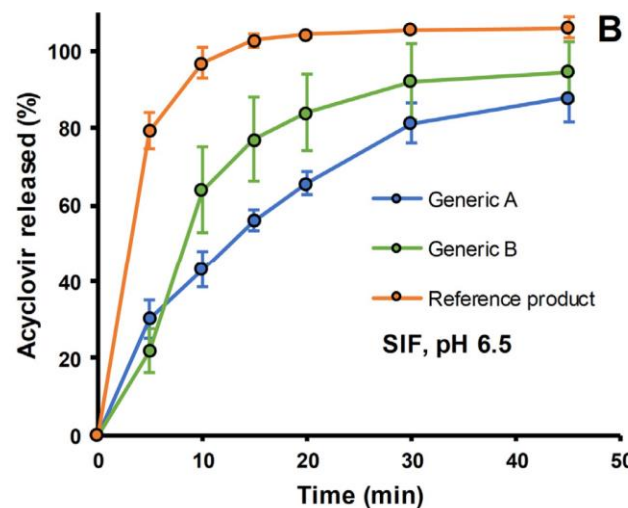
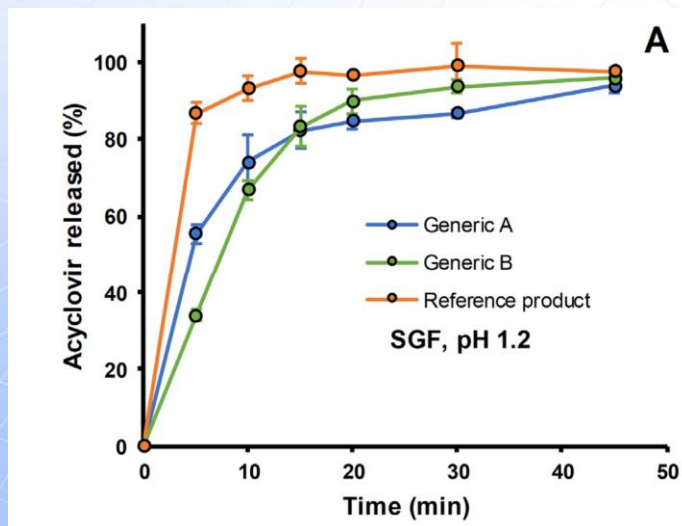


VBE : Test vs Ref : BE predicted



Case study 2: Acyclovir safe space ^A

- BCS class 3-4 drug, weak base (pKa 2.27) in physiological region. $P_{eff} \approx 0.3 \cdot 10^{-4}$ cm/s, Solub 2.33 mg/mL @ pH 5.8, max oral dose = 800 mg
- Distribution and elimination subject to transporters (OCT1) showing polymorphism across populations
- Bioequivalent products show different dissolution profiles



USP2, 50 rpm, 900mL
f2 <50

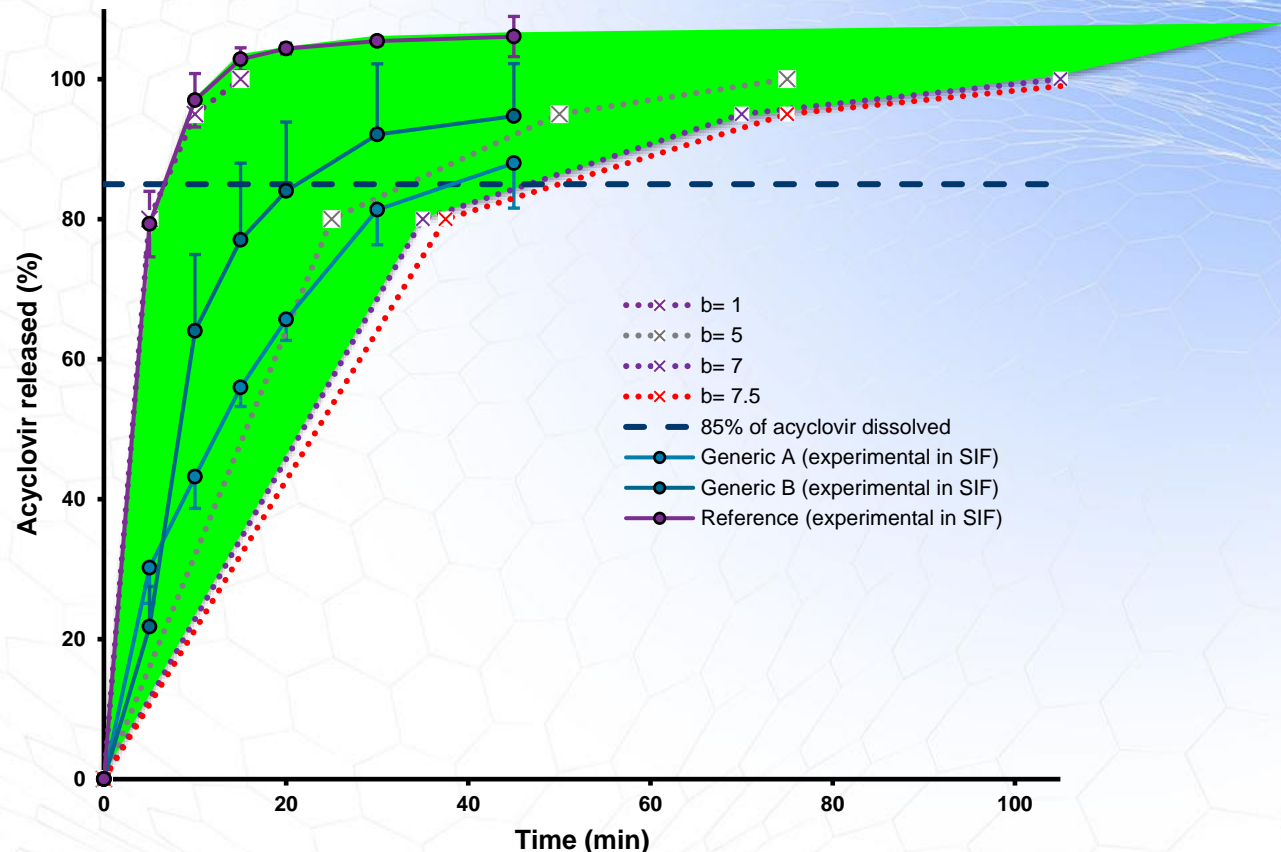
No major difference in excipients
No excipient acting on GI
physiology or permeability
SIF data used as input in PBBM
(direct input of dissolution)

A: García, M.A., et al., Predicting Pharmacokinetics of Multisource Acyclovir Oral Products Through Physiologically Based Biopharmaceutics Modeling. Journal of Pharmaceutical Sciences, 2022. 111(1): p. 262-273.

Case study 2: Acyclovir safe space ^A

- SIF data stretched with time
 $t_{new} = b \times t_{ref}$
- Profiles used to predict PK
- GMR = 0.9 taken as potentially BE

	Ratio of means (T/R)		
Time-scaling	C_{max}	AUC_{0-inf}	AUC_{0-t}
b=1	0.997	0.996	0.996
b=5	0.944	0.937	0.937
b=7	0.904	0.901	0.900
b=7.5	0.894	0.891	0.890
b=10	0.839	0.844	0.843

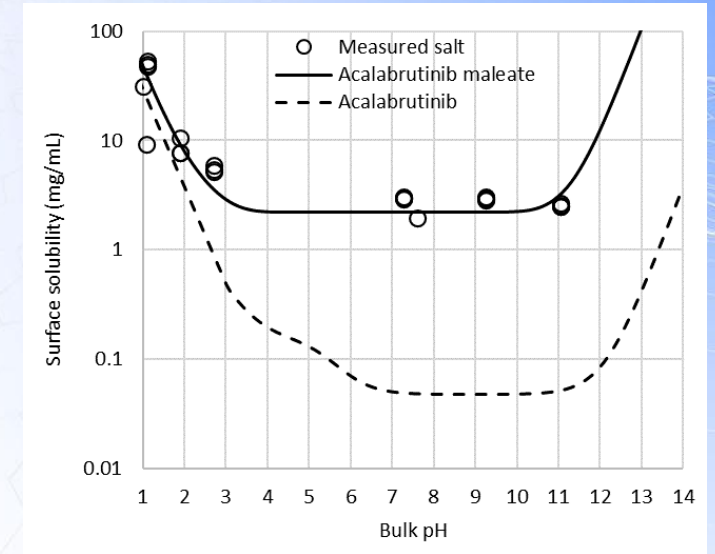


BCS 3 or 4 safe space subject to checking effect of excipients on permeability/GI functions

Case 3 : Acalabrutinib maleate tablet (AMT)

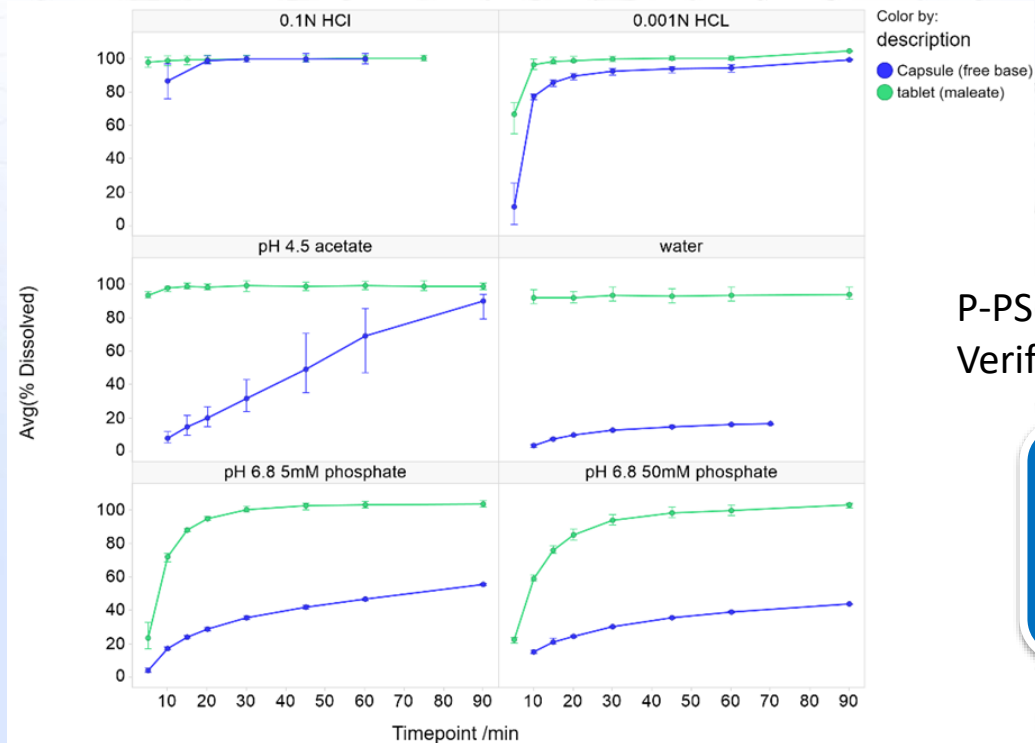
- Project information

- Acalabrutinib free base is associated with label restriction for patients undergoing acid reducing agent (ARA) treatment
- 20-40% hematological cancer patients are estimated to take ARAs
- Acalabrutinib maleate increases surface solubility compared to the free base leading to faster and complete dissolution in all media



- Model purpose

- Justify proposed dissolution specification for AMT

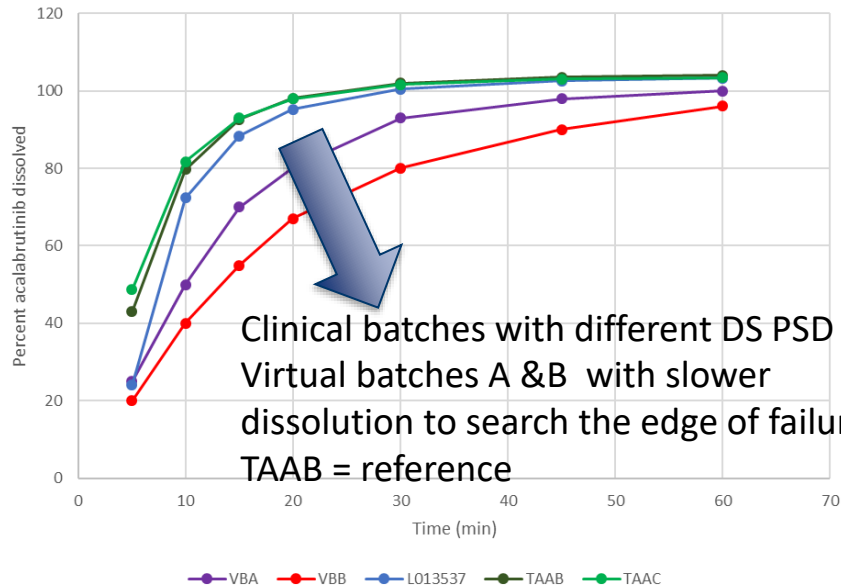


P-PSD used based on 5mM phosphate pH 6.8 data
Verification that other pH could be predicted

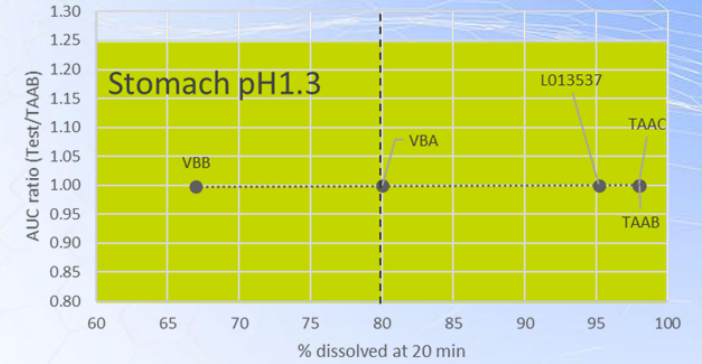
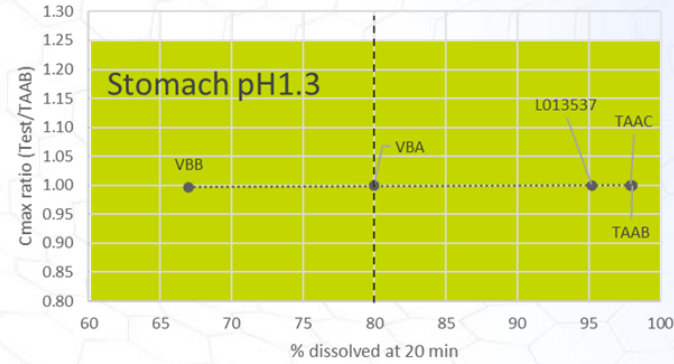
Measurement of BTK occupancy for BE and rel BE studies

AMT : PBBM use

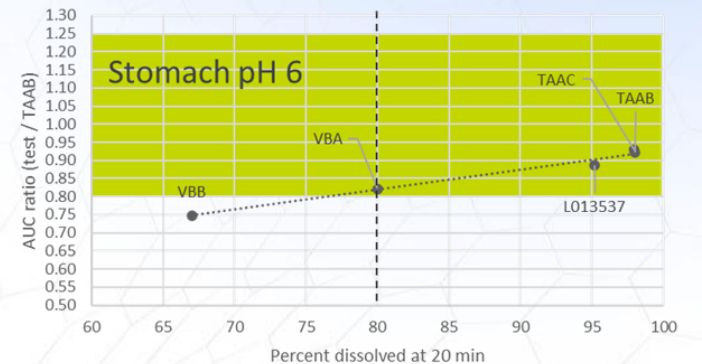
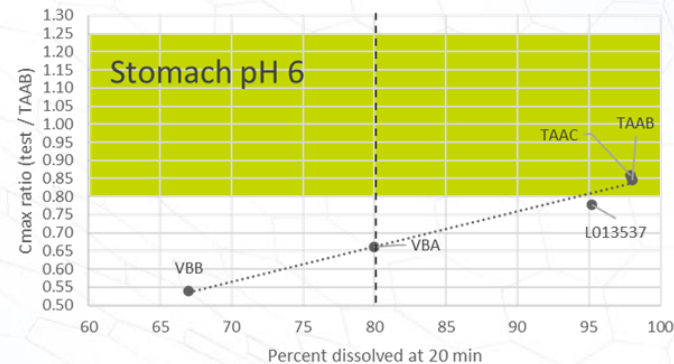
In vitro dissolution with QC method



VBA: Virtual batch A
VBB: Virtual batch B

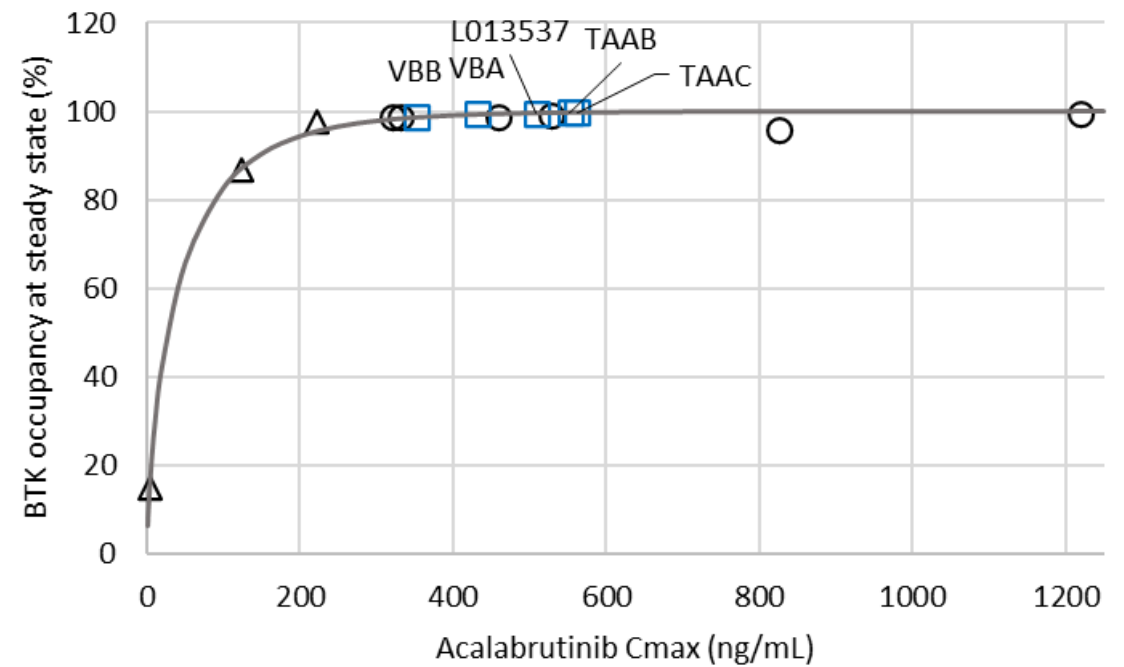
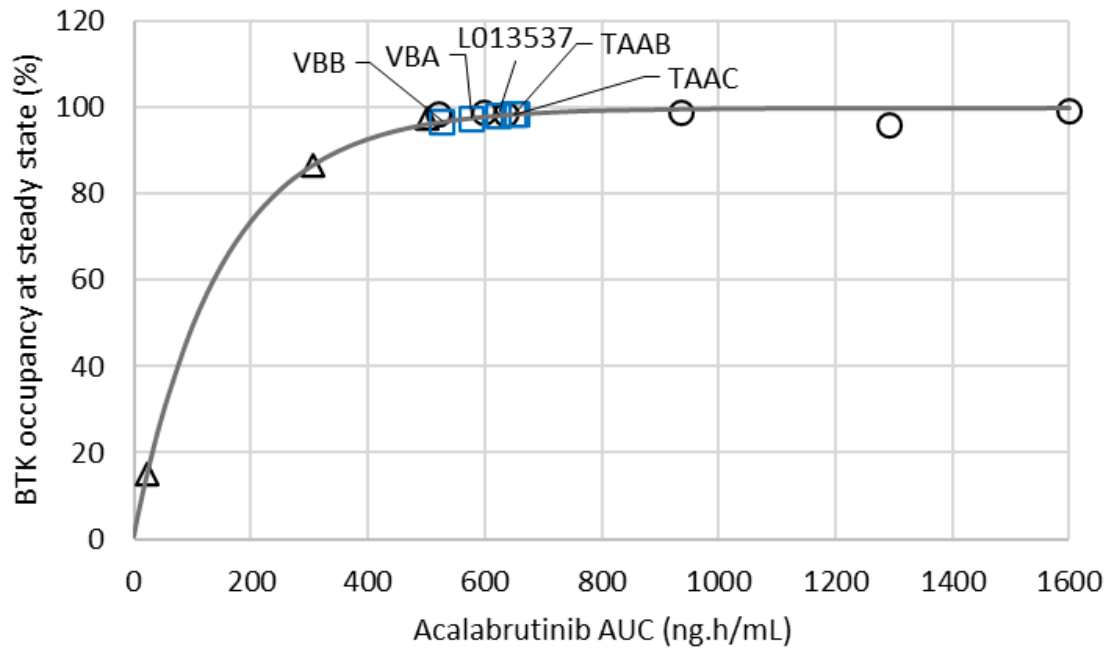


VBA and VBB
bioequivalent to
reference in acidic
stomach conditions



VBA and VBB with
PPI not BE to
reference (in acidic
conditions)

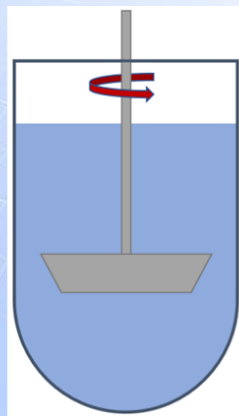
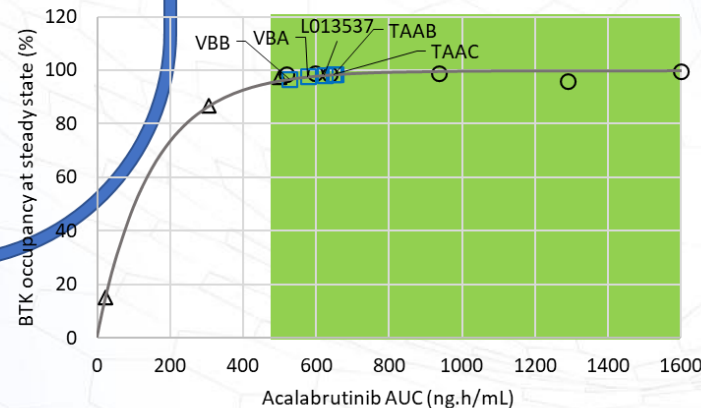
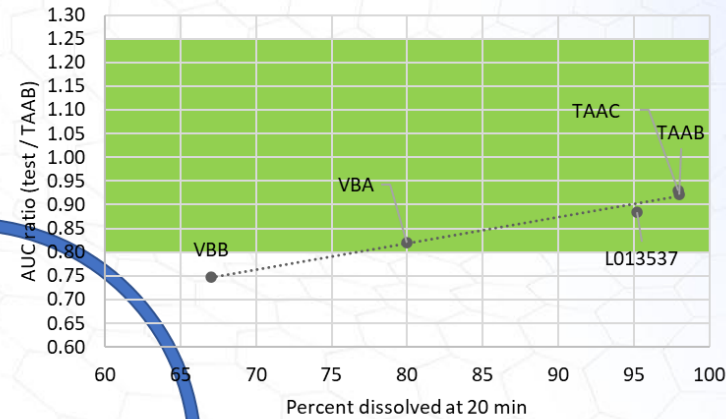
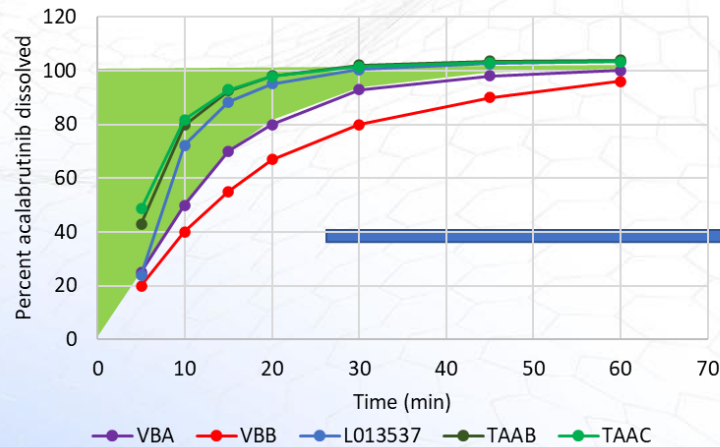
AMT : PBBM + PKPD model



BTK-occupancy vs AUC or vs Cmax, show that exposure to VBA or VBB in neutral stomach conditions are anticipated to be safe and effective :
Similar target engagement compared to pivotal efficacy study

Acalabrutinib maleate tablet: conclusions

- VBA was used to delineate dissolution safe space identified using PBBM and PKPD



**DP dissolution
Specification**

Q=80% 20-30 minutes is anticipated to be safe and effective for 100 mg AMT
Oral solution extemporaneously prepared from tablet was administered in the clinic and proved BE to the tablet (upper bound of safe space)

Take-home messages

- PBBM can be used with in vitro dissolution to run VBE studies and determine edge of failure
 - CQA translate to dissolution. Dissolution used as input (method to be justified)
 - Size of VBE should be adapted to the within subject variability
 - Recommendation : Ensure all VBEs are successful when comparing reference to reference
- PBBM and PKPD/PKTD can be used to justify for a larger safe space based on product efficacy/safety even if they are not bioequivalent
 - Need to measure biomarker in the clinic
 - Need “clean” PK-PD PK-Tox relationships
- Low permeability compounds may have a large safe space unrelated to product dissolution
 - Need to check impact of excipients on GI function/permeability

Thanks

