SimulationsPlus

BO Session I : Safe space(s)

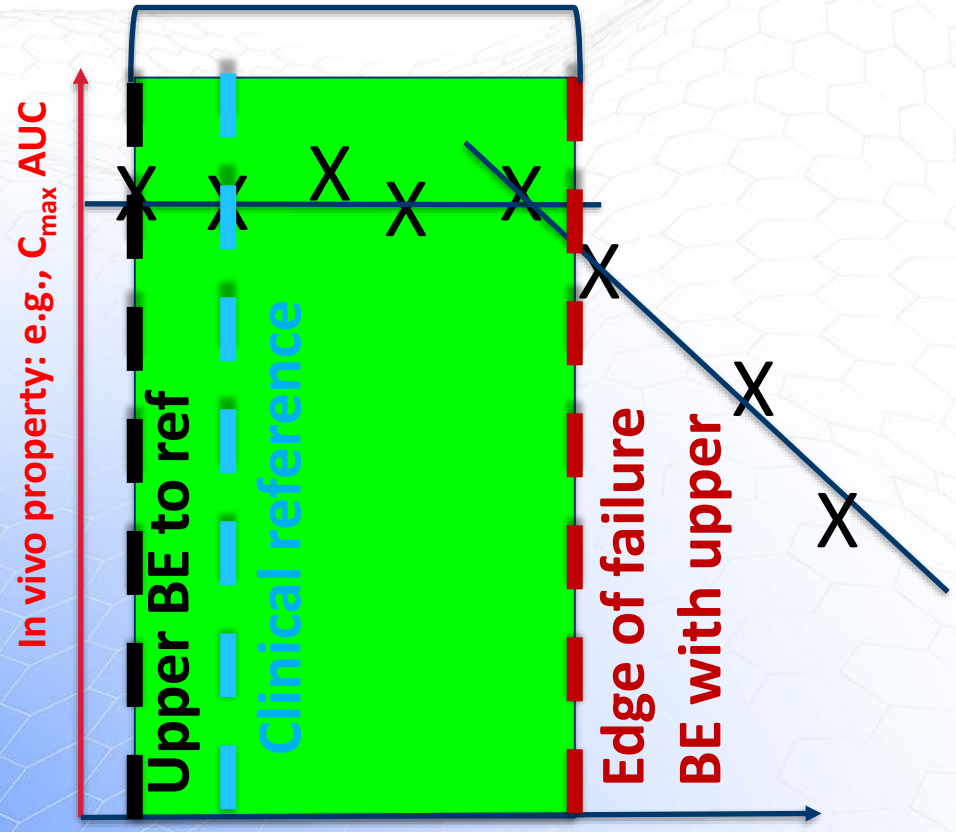
M-CERSI workshop

Xavier Pepin

2023 August 30

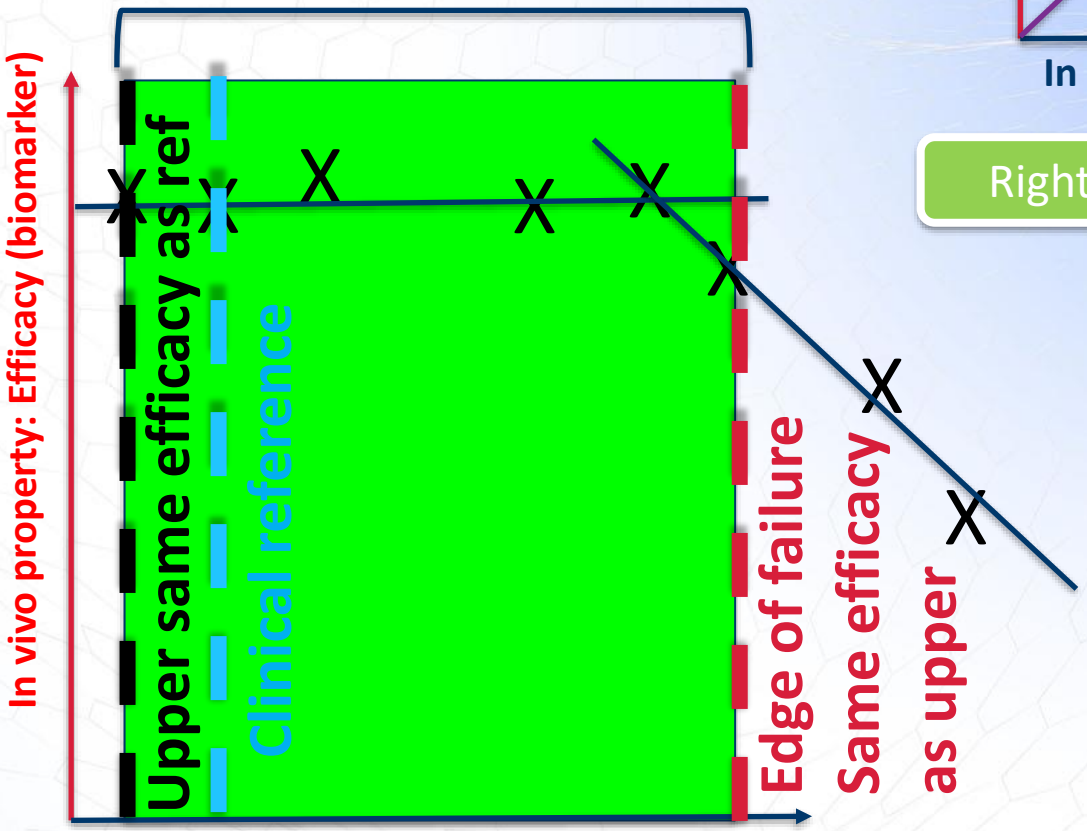
Safe space(s)

Safe space based on BE

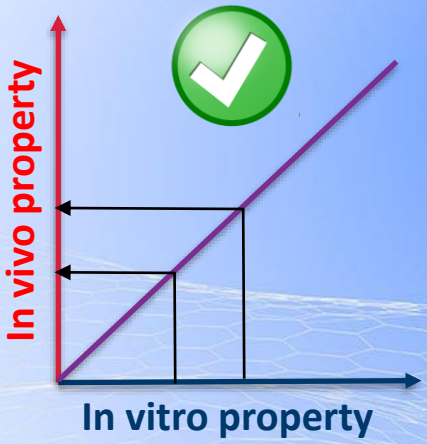


CBA: e.g. Particle size, T80% dissolution, compression force

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

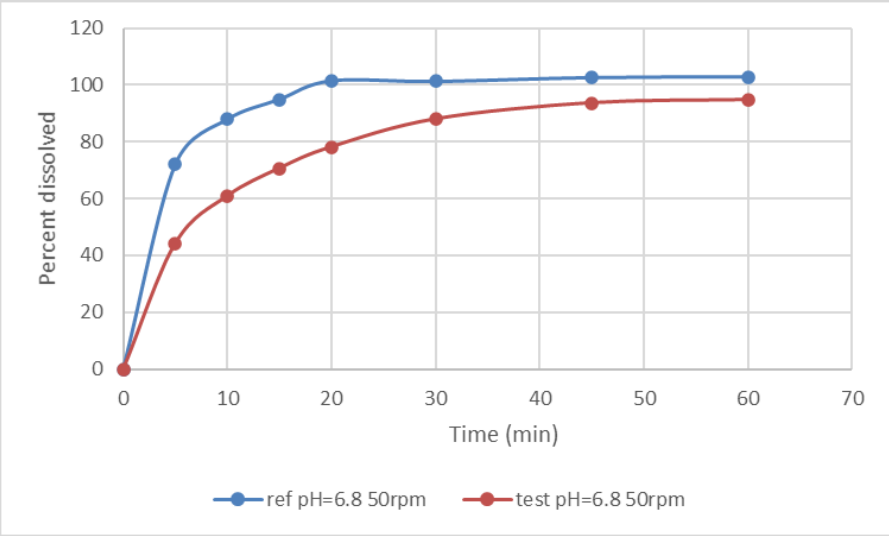
- PBBM+PKPD based safe space
  - Perform sensitivity analyses to determine GMR evolution with CBA
  - Check size of BE safe space (see above)
  - Predict efficacy across all exposure (Cmax and AUC) using PBBM and PKPD + PKTD
  - Predict the edge of failure based on efficacy and tox
  - Conclude on the 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



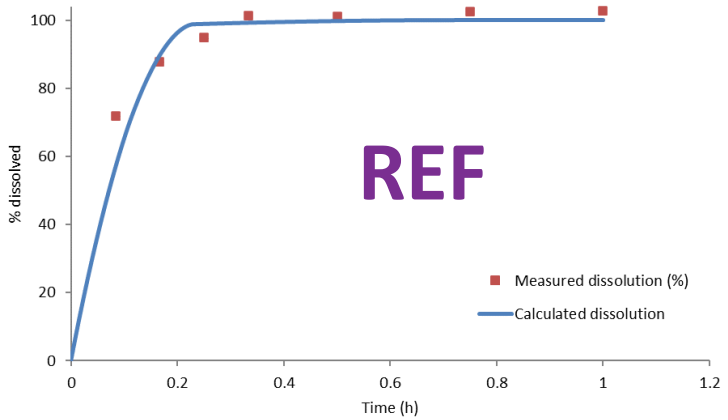
Use of VBE study to predict bioequivalence = same process as for edge of failure determination
Real batches could be virtual batches representative of process capability !

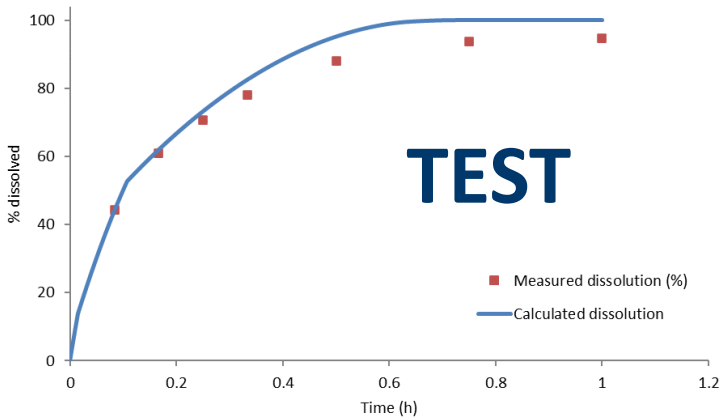
Mechanistic integration of dissolution

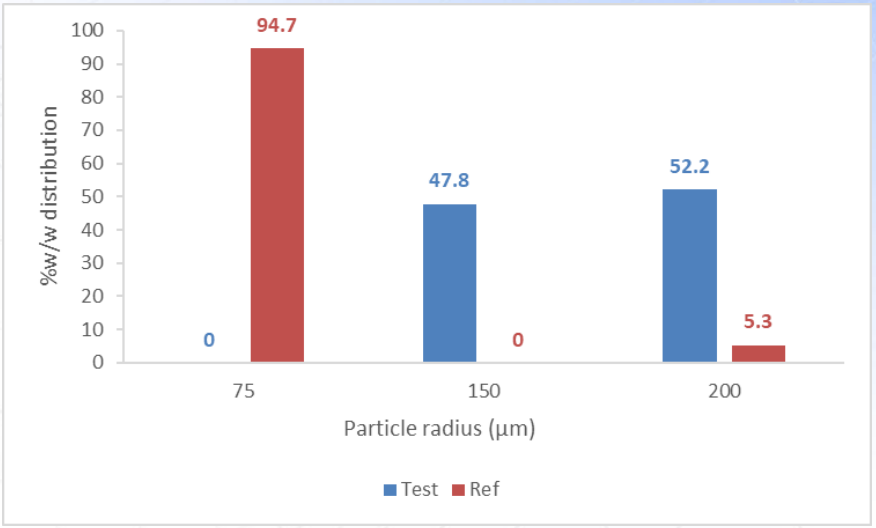
IR products are sensitive to pH, volume, transit time

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

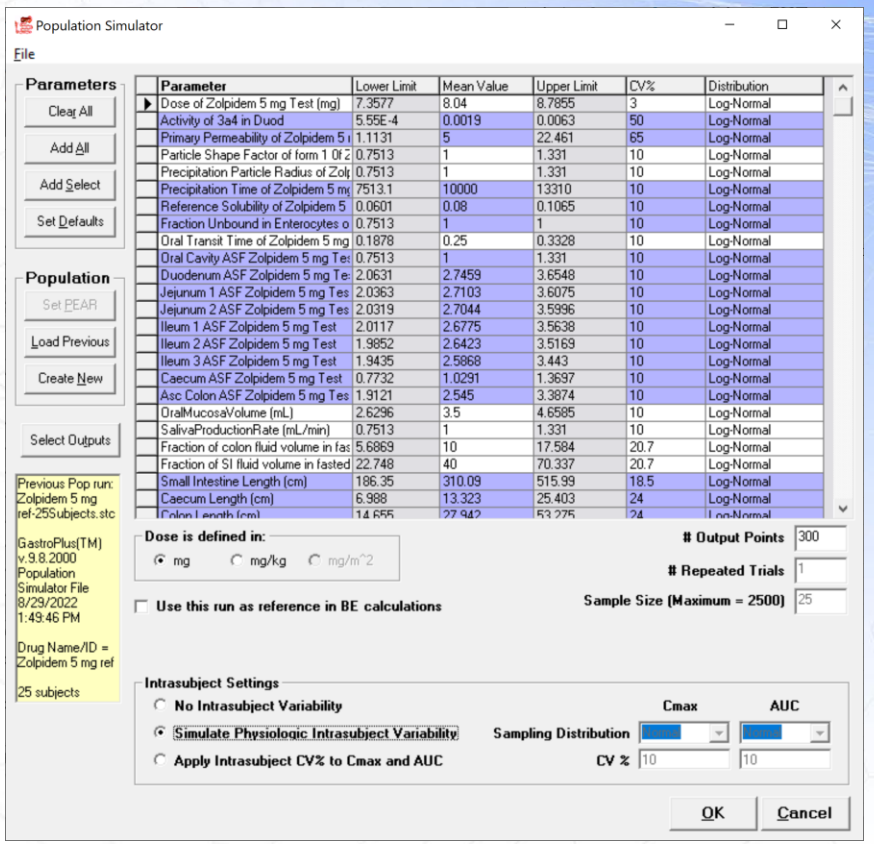
B: Pepin, X., M. Goetschy, and S. Abrahmsén-Alami, Mechanistic models for USP2 dissolution apparatus, including fluid hydrodynamics and sedimentation. Journal of Pharmaceutical Sciences, 2021. https://doi.org/10.1016/j.xphs.2021.10.006

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

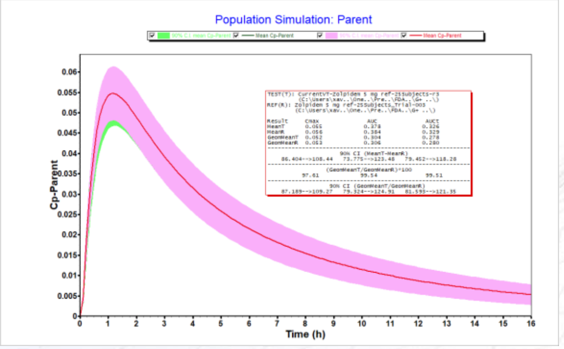
VBE : Virtual BE testing

- N=10 trials of n=25 subjects (default)
- Ref = current 5 mg tablet
- Test = ODT tablet
- Cross over trials with physiological variability

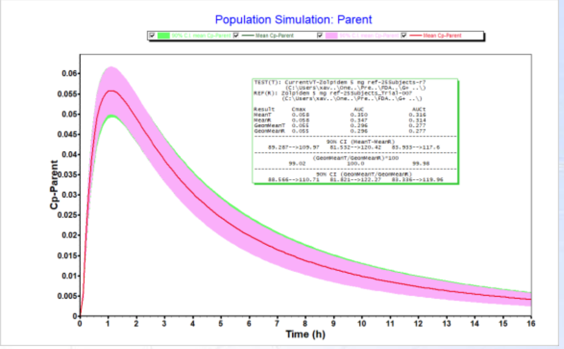
- 1st trial : Ref vs Ref : See if the within subject variability is not too high vs # of subjects per study



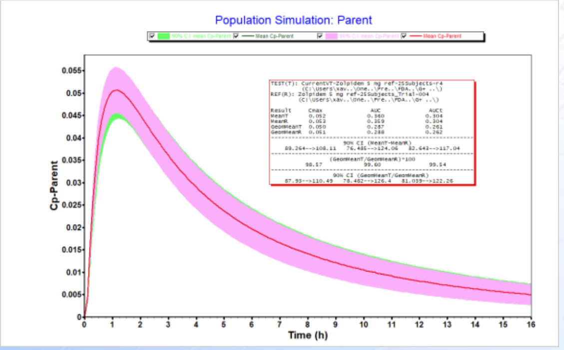
VBE : Ref vs Ref : failure to demonstrate BE with n=25

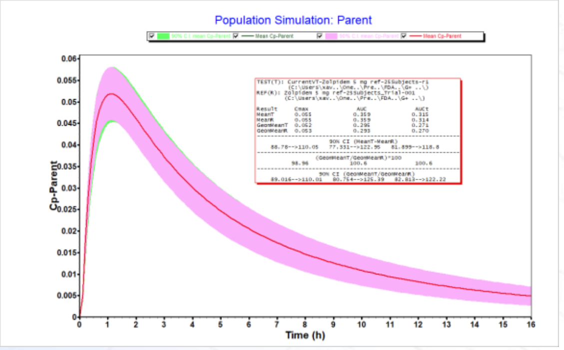


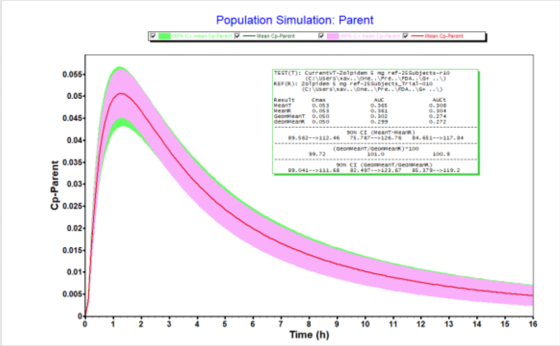
5 studies failed
5 studies passed

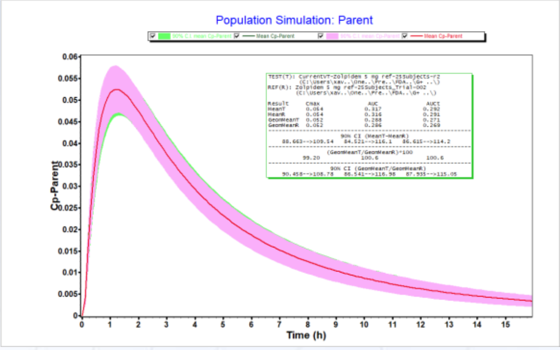


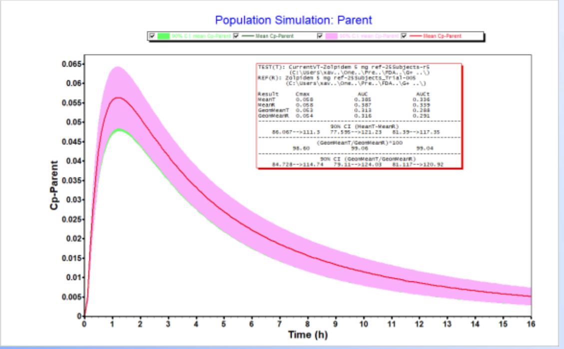
Within subject variability of 30%

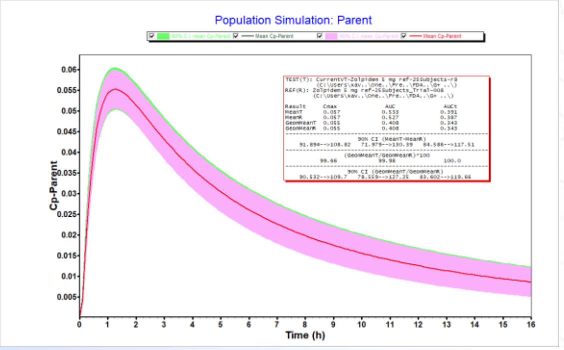


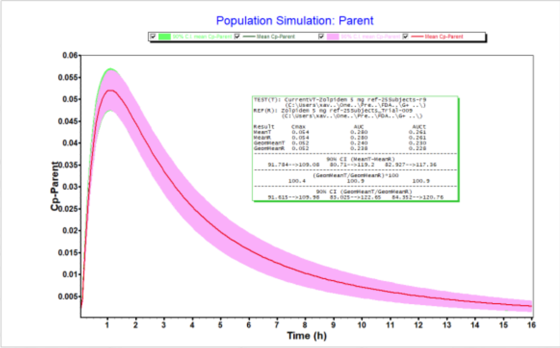


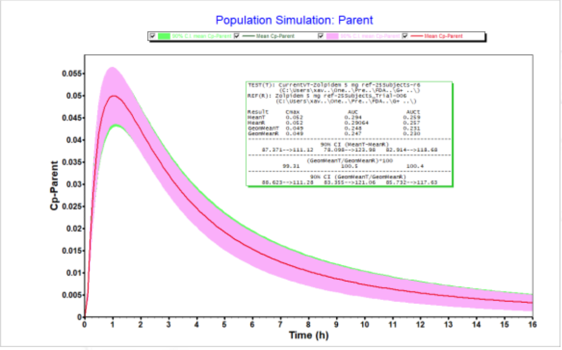






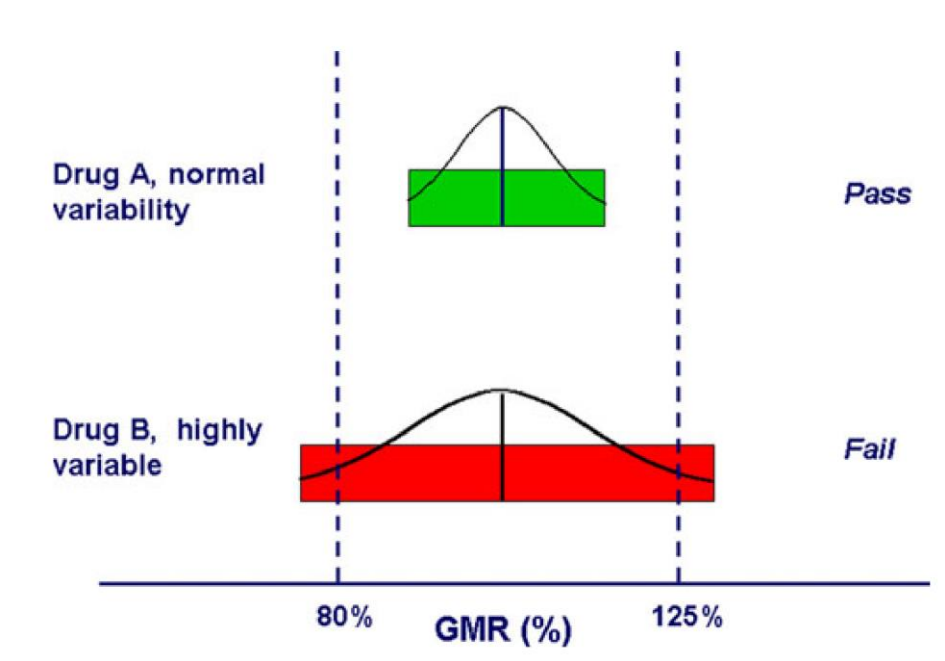






VBE : Need to power the study to demonstrate BE

Within subject variability of 30%



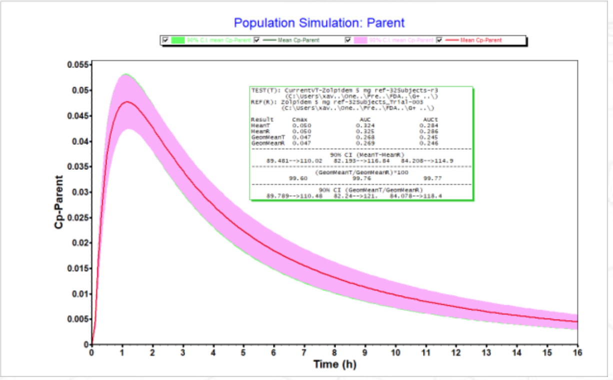
Within-subject %CV	GMR (%)	Sample size for a two-way crossover study
15	100	10
	105	12
	110	20
30	100	32
	105	38
	110	68
45	100	66
	105	80
	110	142
60	100	108
	105	132
	110	236
75	100	156
	105	190
	110	340

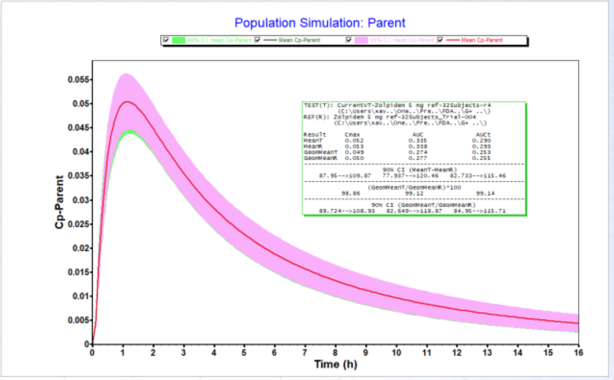
Need 32 subjects to demonstrate BE for the same formulation with 30% Within-S %CV

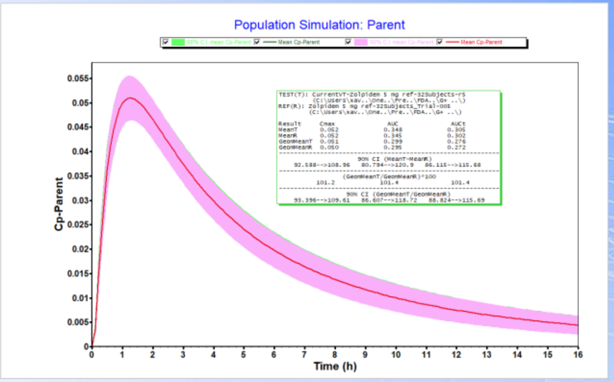
Davit, B., et al., Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. The AAPS Journal, 2012. 14(4): p. 915-924. http://dx.doi.org/10.1208/s12248-012-9406-x

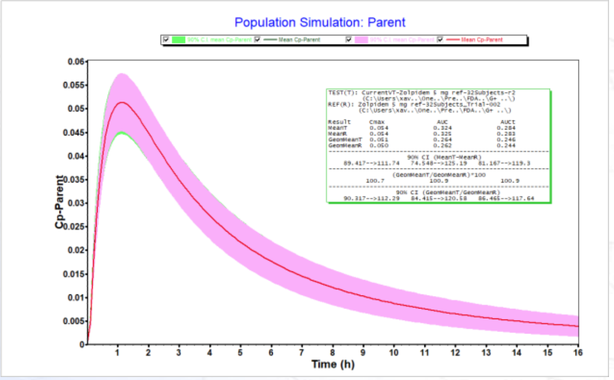
VBE : Ref vs Ref : BE with n=32

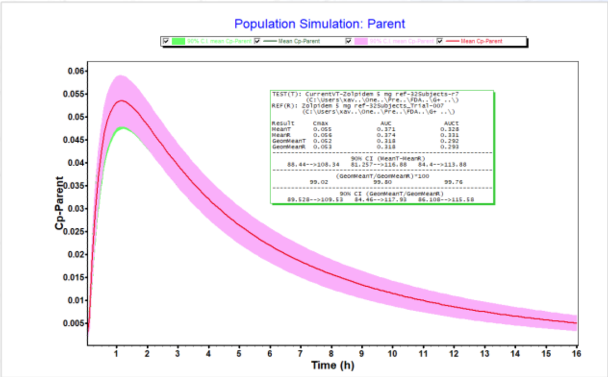
N=32 subject enough to demonstrate BE with the same formulation

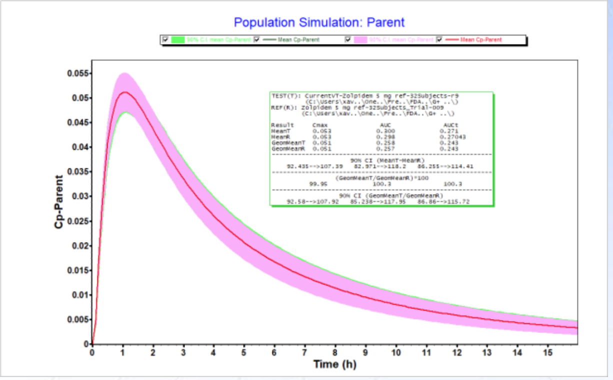


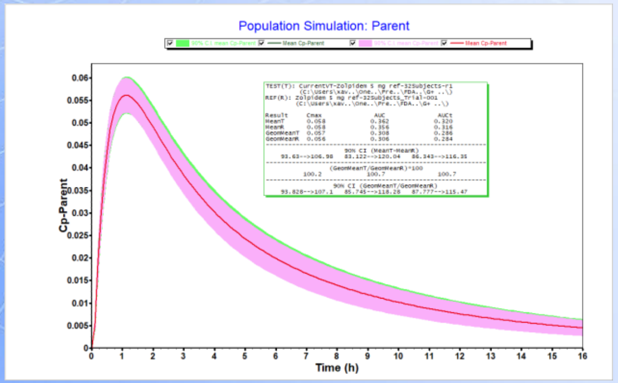


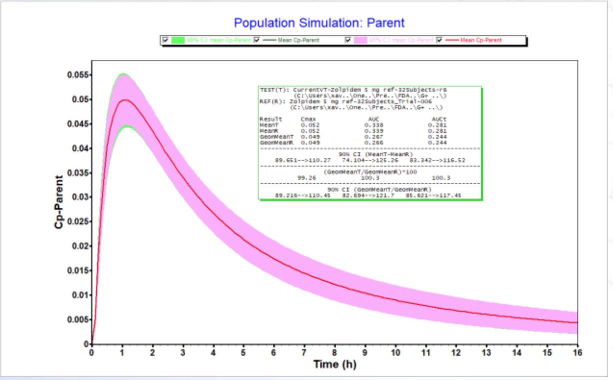


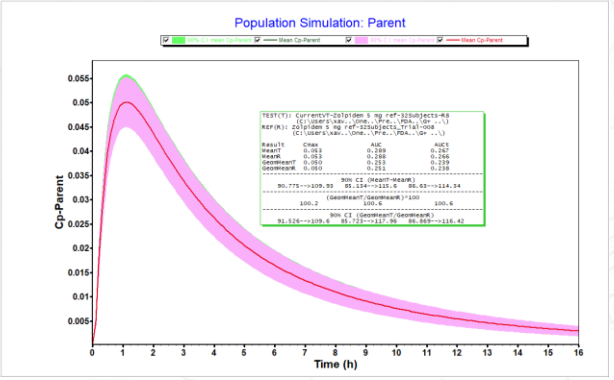


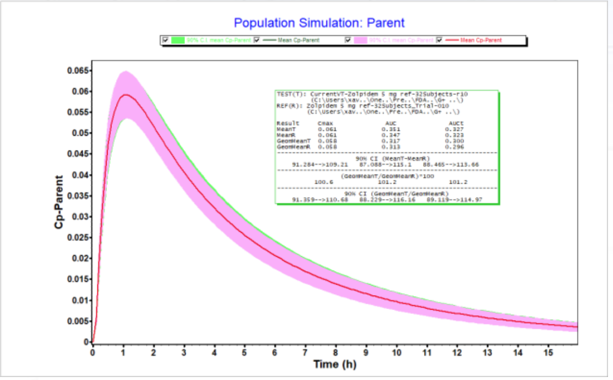




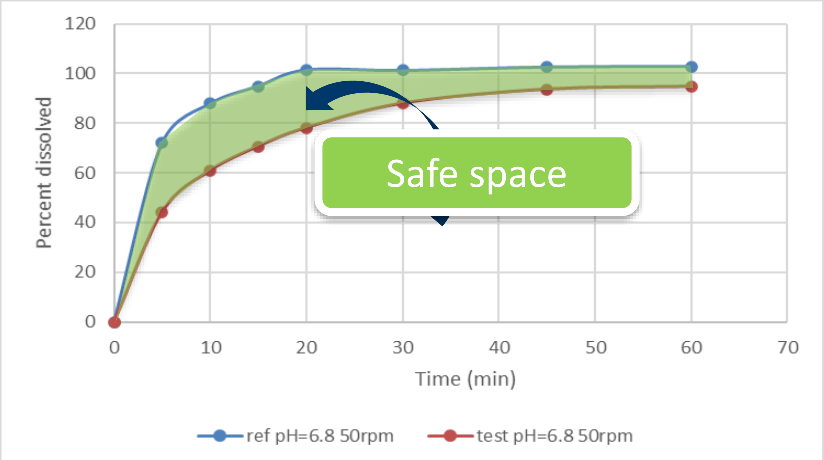


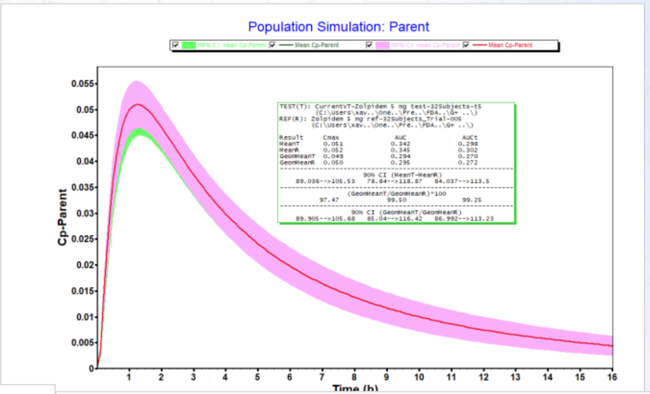


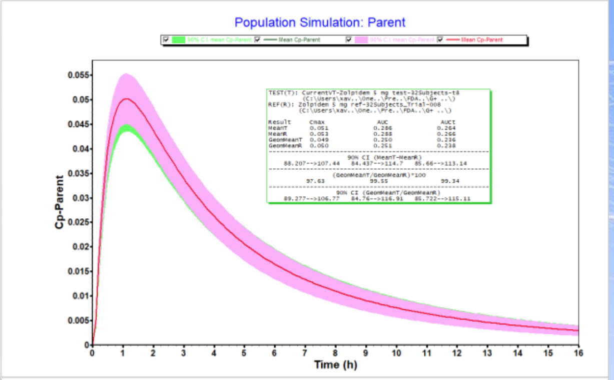


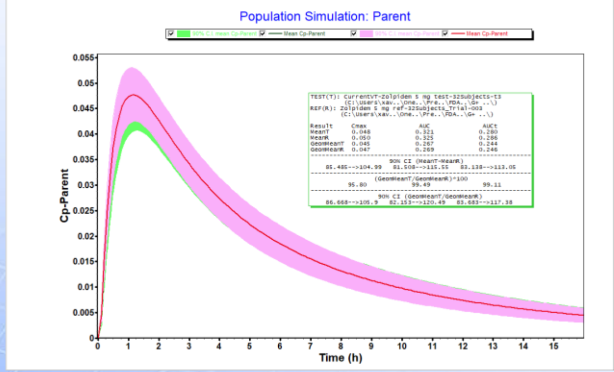


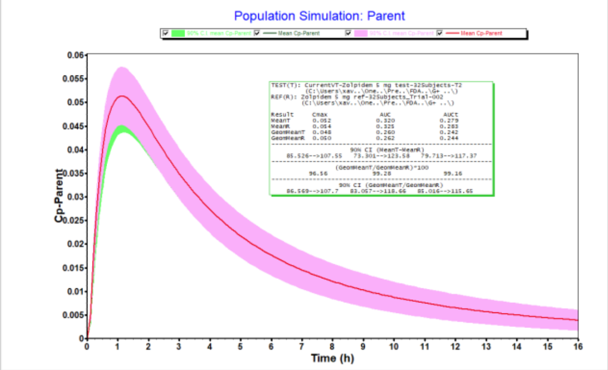
VBE : Test vs Ref : BE predicted

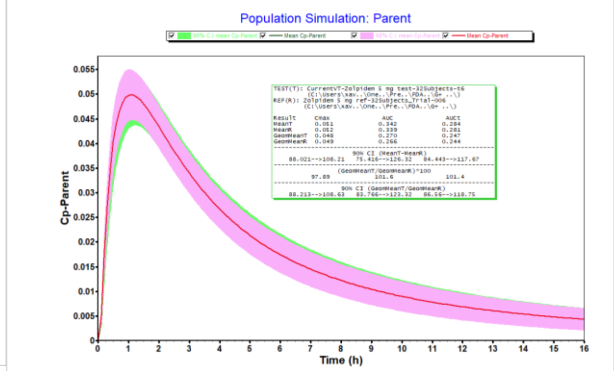


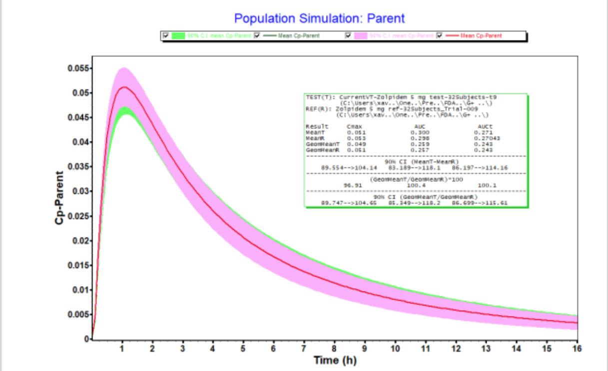


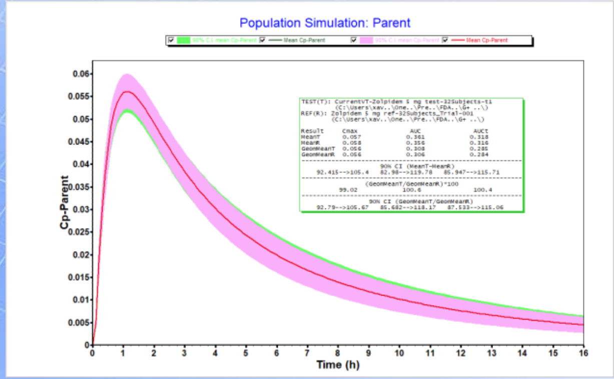


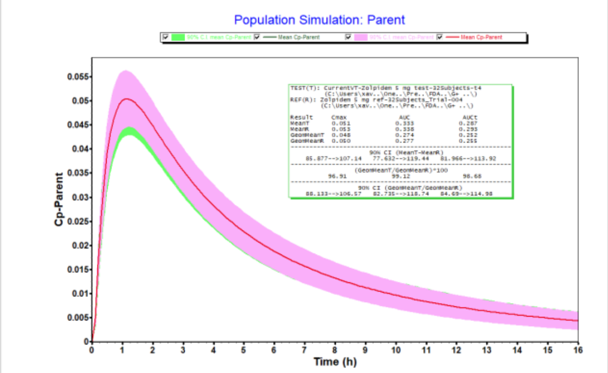


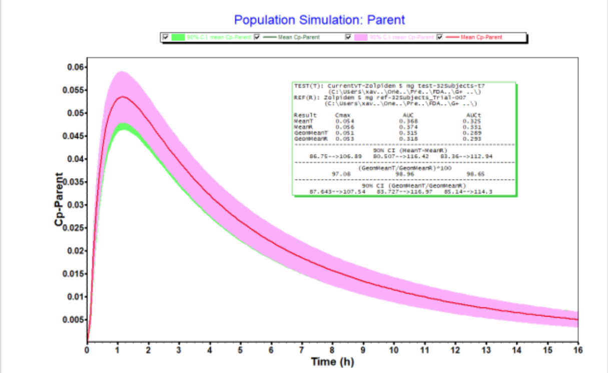


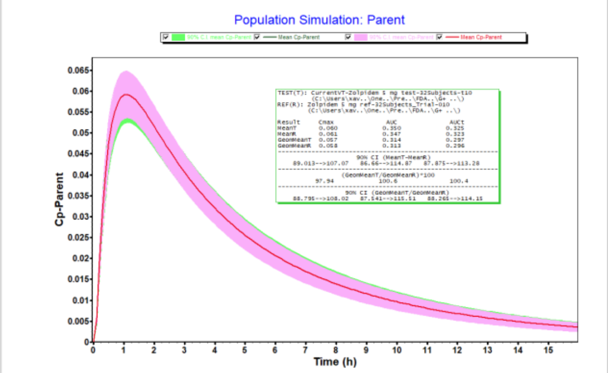






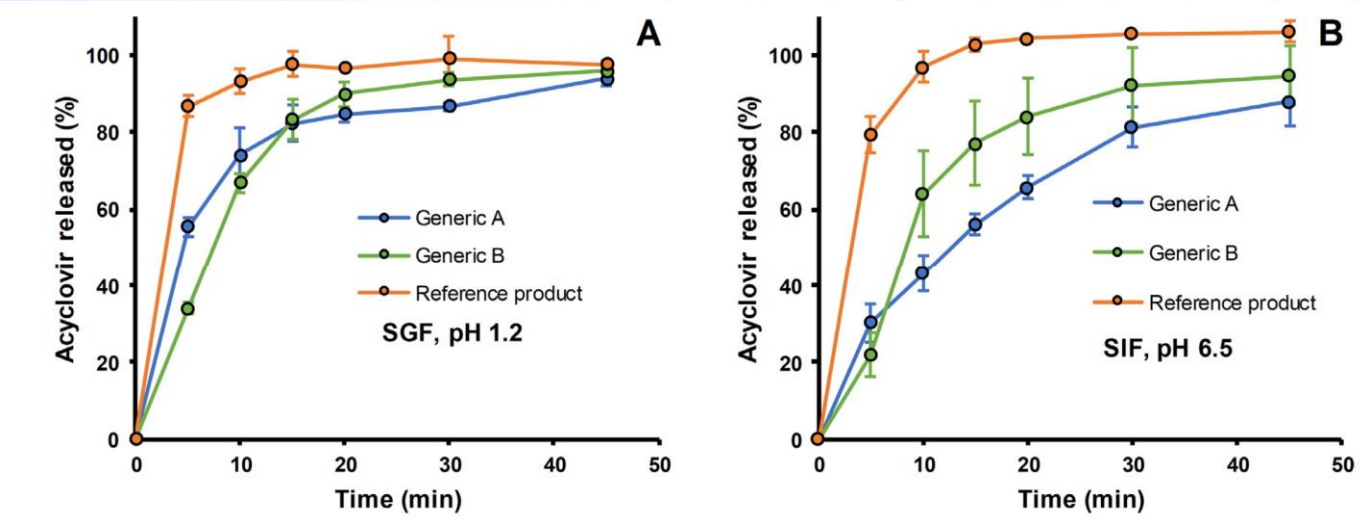






Case study 2: Acyclovir safe space [A]

- BCS class 3-4 drug, weak base (pKa 2.27) in physiological region. Peff ≈0.3 10^{-4} cm/s, Solub 2.33 mg/mL @ pH5.8, max oral dose = 800 mg
- Distribution and elimination subject to transporters (OCT1) showing polymorphism across populations
- Bioequivalent products show different dissolution profiles



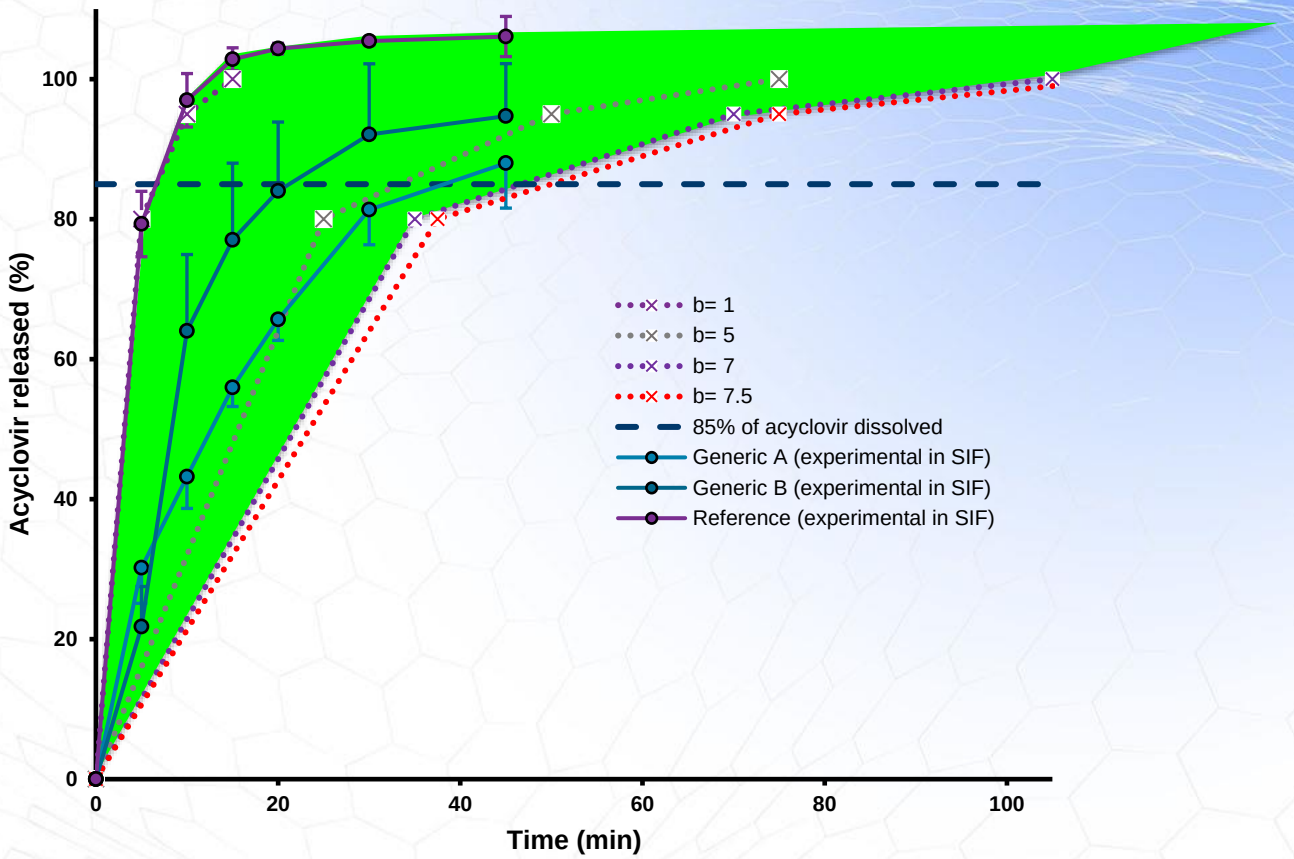
USP2, 50 rpm, 900mL
f2 <50
No major difference in excipients
No excipient acting on GI physiology or permeability
SIF data used as input in PBBM (direct input of dissolution)

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

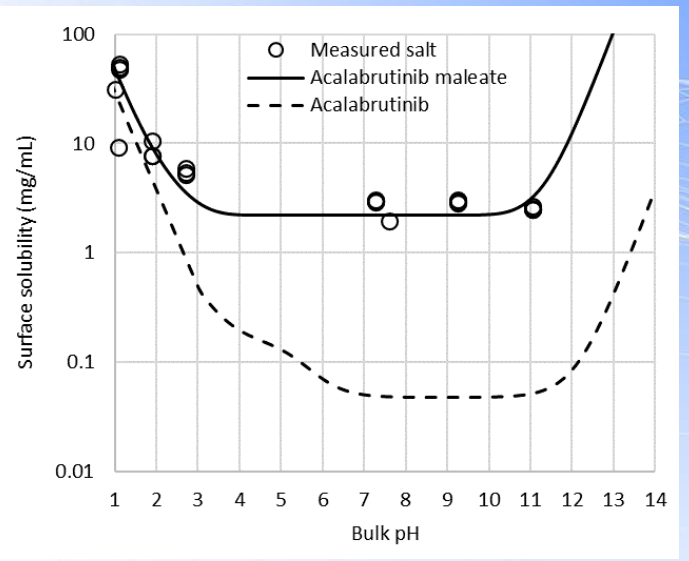
	Ratio of means (T/R)		
Time-scaling	C_{max}	$AUC_{0\text{-inf}}$	$AUC_{0\text{-t}}$
b=1	0.997	0.996	0.996
b=5	0.944	0.937	0.937
b=7	0.904	0.901	0.900
b=7.5	0.894	0.891	0.890
b=10	0.839	0.844	0.843



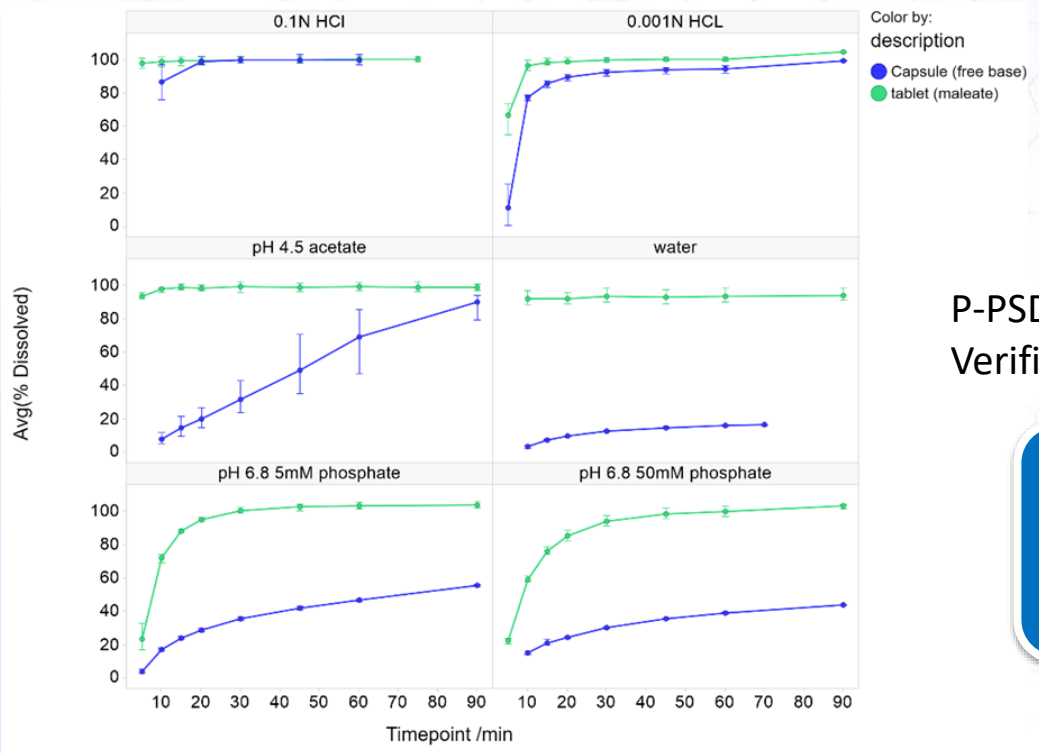
BCS 3 or 4 safe space subject to checking effect of excipients on permeability/GI functions

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



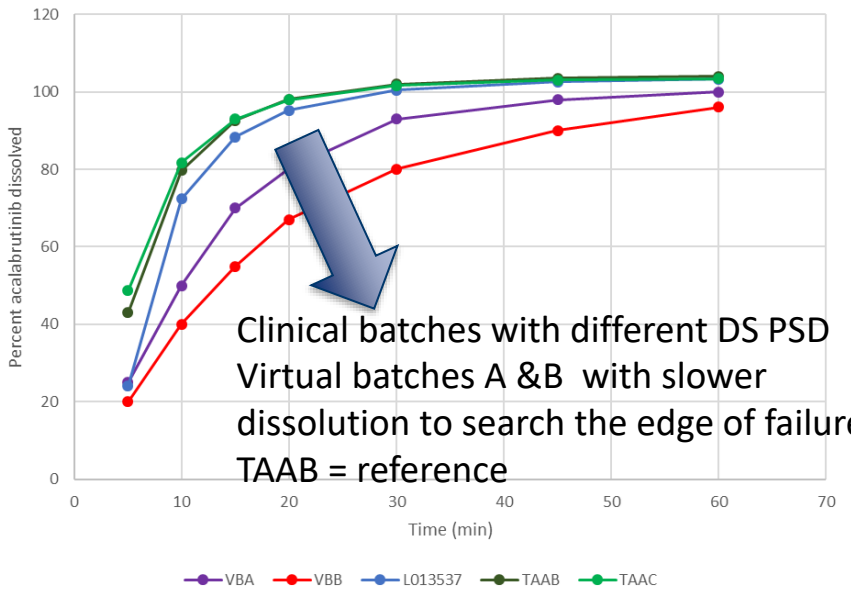
P-PSD used based on 5mM phosphate pH 6.8 data
Verification that other pH could be predicted

Measurement of BTK occupancy for BE and rel BE studies

SimulationsPlus

AMT : PBBM use

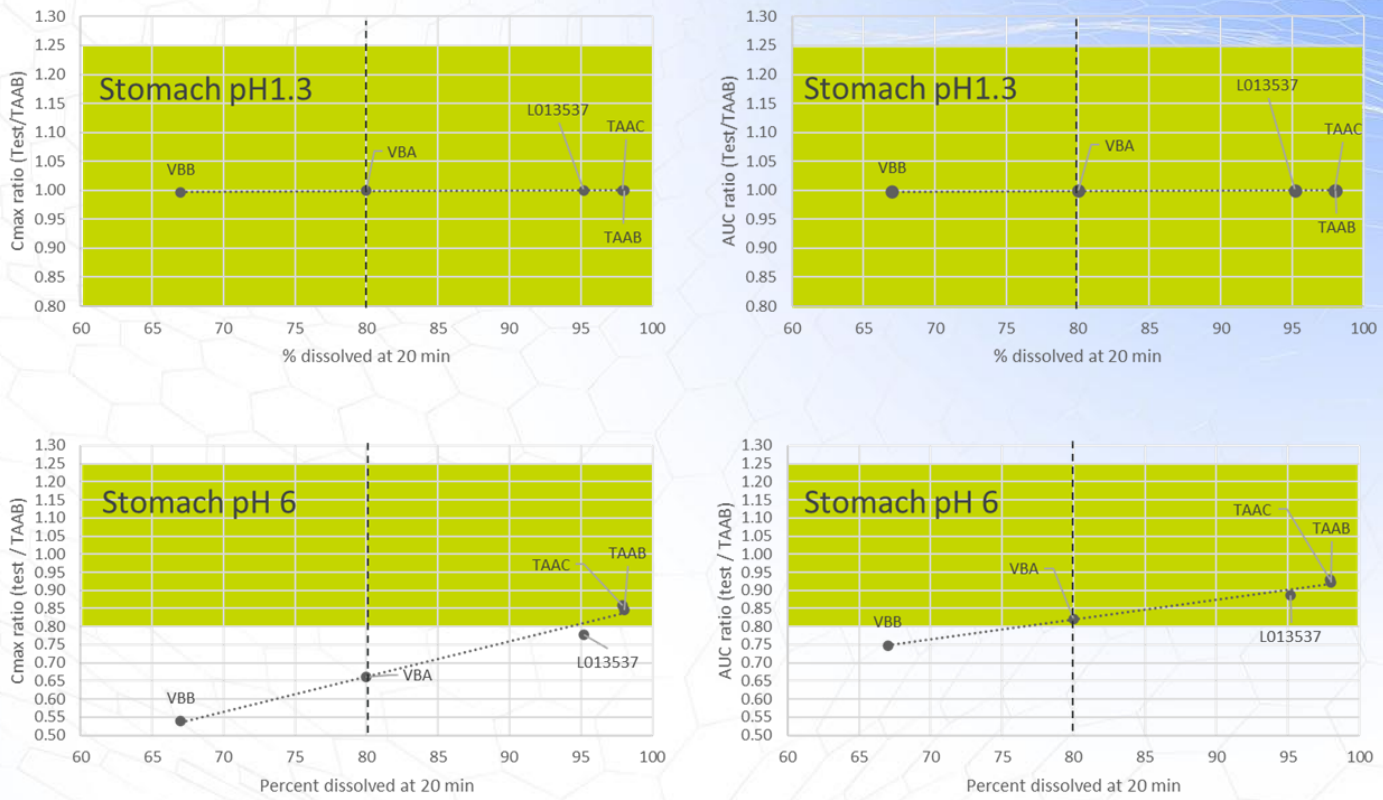
In vitro dissolution with QC method



Clinical batches with different DS PSD
Virtual batches A &B with slower dissolution to search the edge of failure.
TAAB = reference

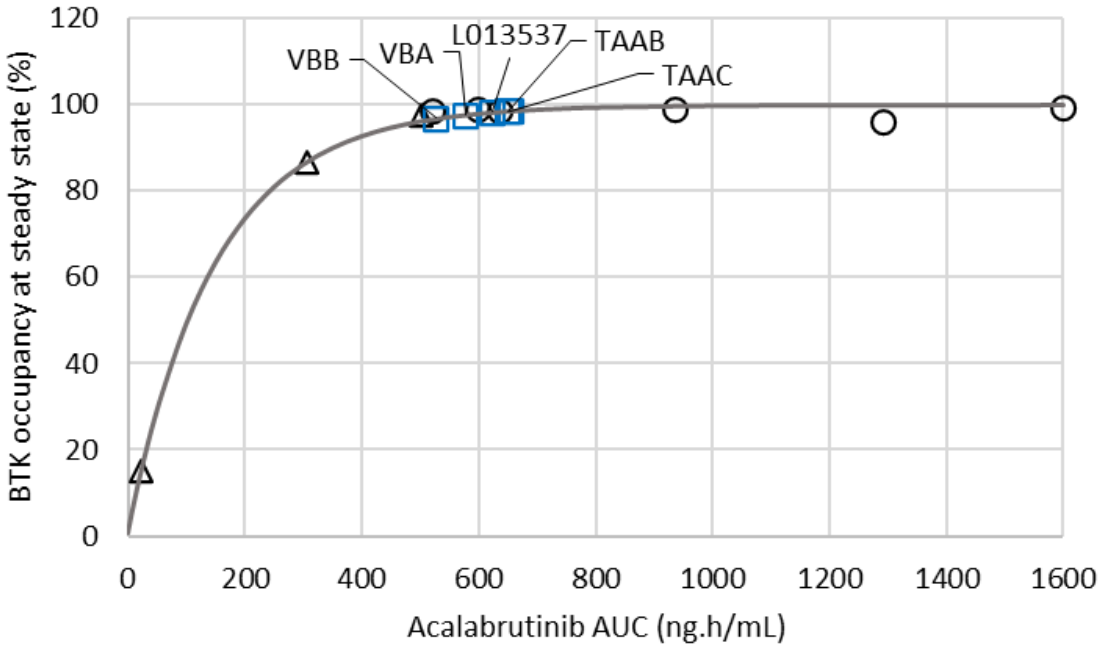
VBA: Virtual batch A
VBB: Virtual batch B

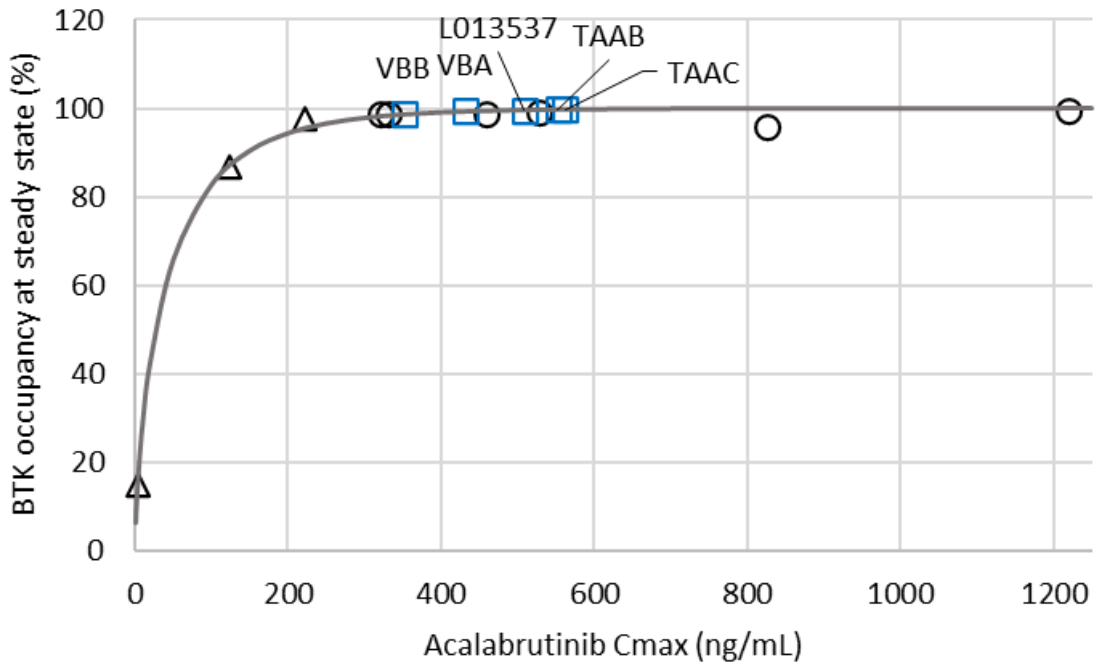
VBA and VBB bioequivalent to reference in acidic stomach conditions



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

AMT : PBBM + PKPD model

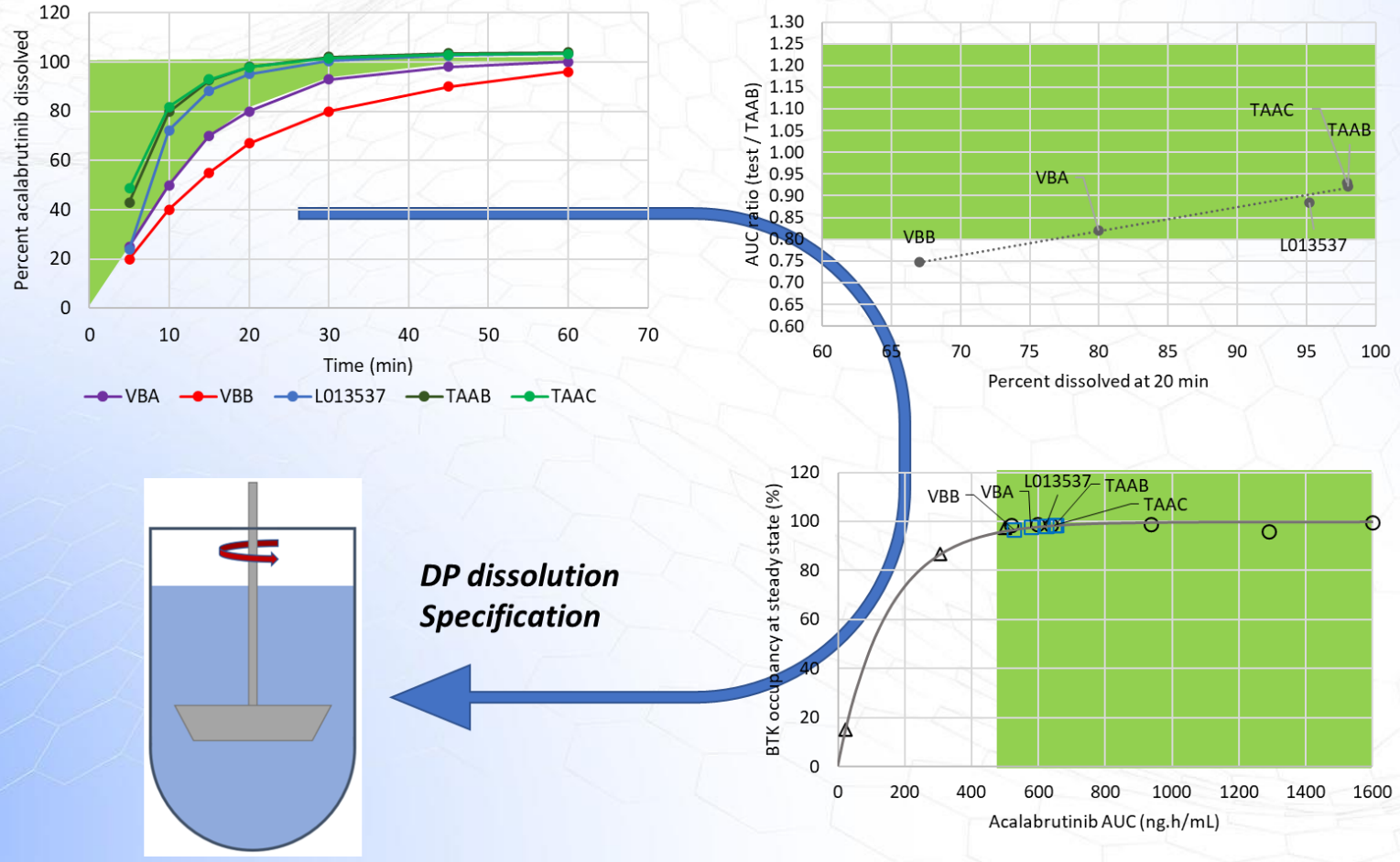




BTK-occupancy vs AUC or vs Cmax, show that exposure to VBA or VBB in neutral stomach conditions are anticipated to be safe and effective : Similar target engagement compared to pivotal efficacy study

Acalabrutinib maleate tablet: conclusions

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



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