Clinical Development, US

Virtual Bioequivalence: Model development, Verification and Applications

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Sandoz Inc. (A Novartis Division)

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Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

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Outline

- Introduction
  - Bioequivalence study
  - Virtual Bioequivalence (VBE)
- Model development & verification using a case study
- 2 examples
- Conclusion

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Bioequivalence (BE) Study

- BE study compares the systemic exposure profile of a test drug product to that of a reference drug product
- For two orally administered drug products to be bioequivalent, the active drug ingredient in the test product must exhibit the same rate (C_{max}) and extent of absorption (AUC) as the reference drug product
- Cross-over PK study, typically in healthy subjects
  - 90% CI of GMR between 80-125% for AUC and C_{max}

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Virtual Bioequivalence (VBE)

- Use of physiological models to predict the outcome of a BE study comparing test and reference formulations
  - Conduct “x” number of virtual trials in a model generated population in crossover manner to assess the outcome of a BE study
- Applications -
  - Predict outcome to support –
    - Formulation changes in late stage clinical development
    - Generic product development
    - Dissolution specification setting
    - Manufacturing site change
    - Waiver of Fed BE study
  - Minimize the number of “pilot” PK studies
  - Provide more confidence in the outcome of a “pivotal” BE study

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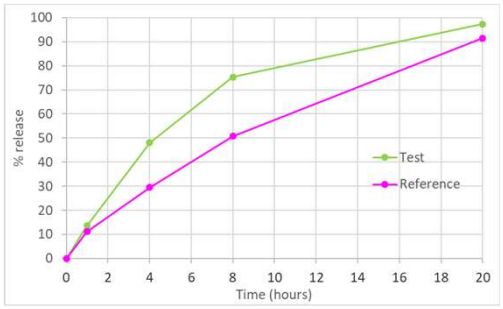
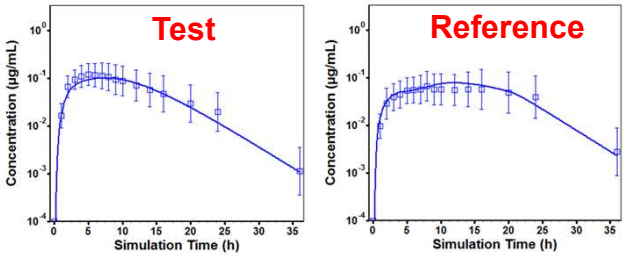


In vitro dissolution data comparing test and reference formulations

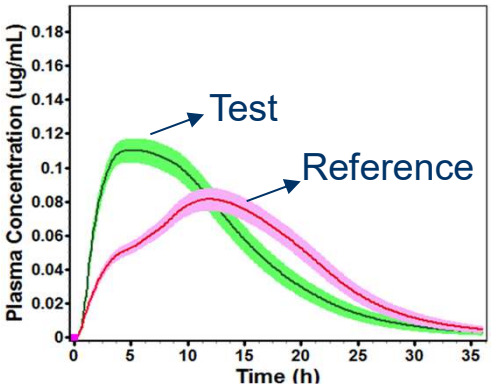
Model built & verified using available data

Conduct appropriate PSA

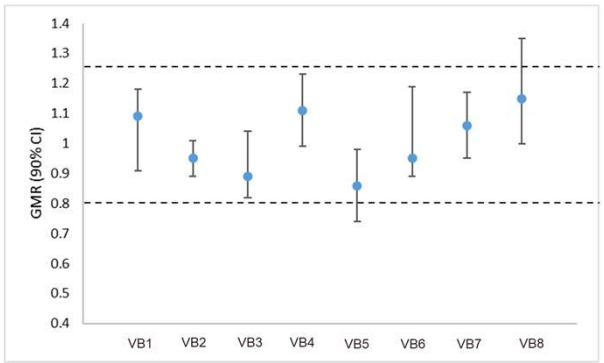


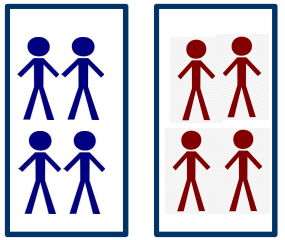
Predicted plasma PK profile and comparison with observed data

Virtual Bioequivalence



Virtual trial output comparing test and reference formulation





Cross-over population simulation by incorporating variability in PK parameters from previous clinical data

Mitra et al, Eu J Pharm BioPharm. 134, 117-125 (2019)

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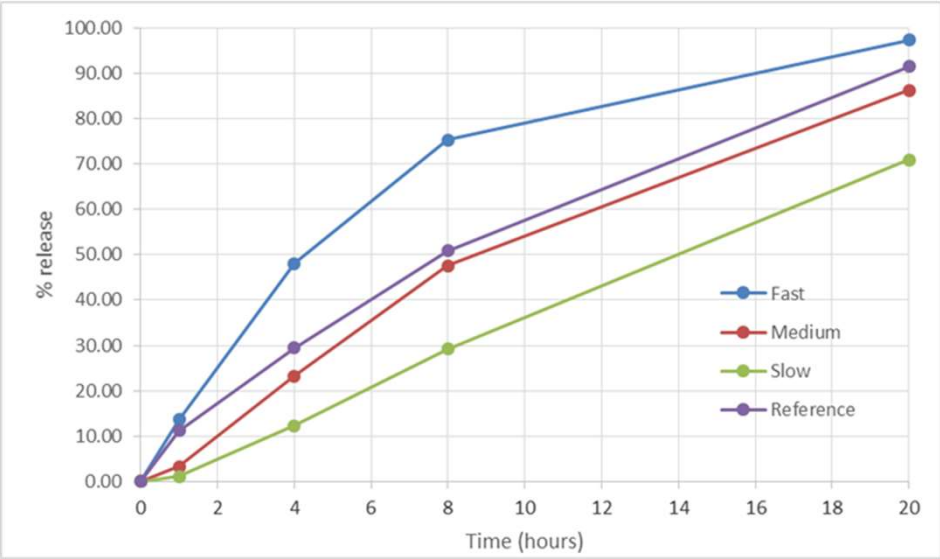
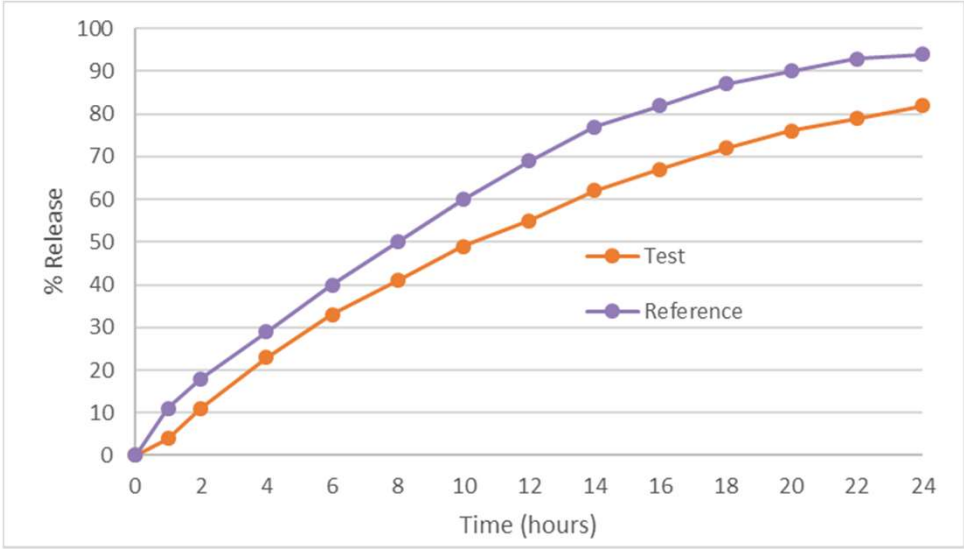
Virtual BE for Controlled Release Formulation

- BCS 1 compound
- Controlled Release formulation

Pilot formulations



Pivotal formulation



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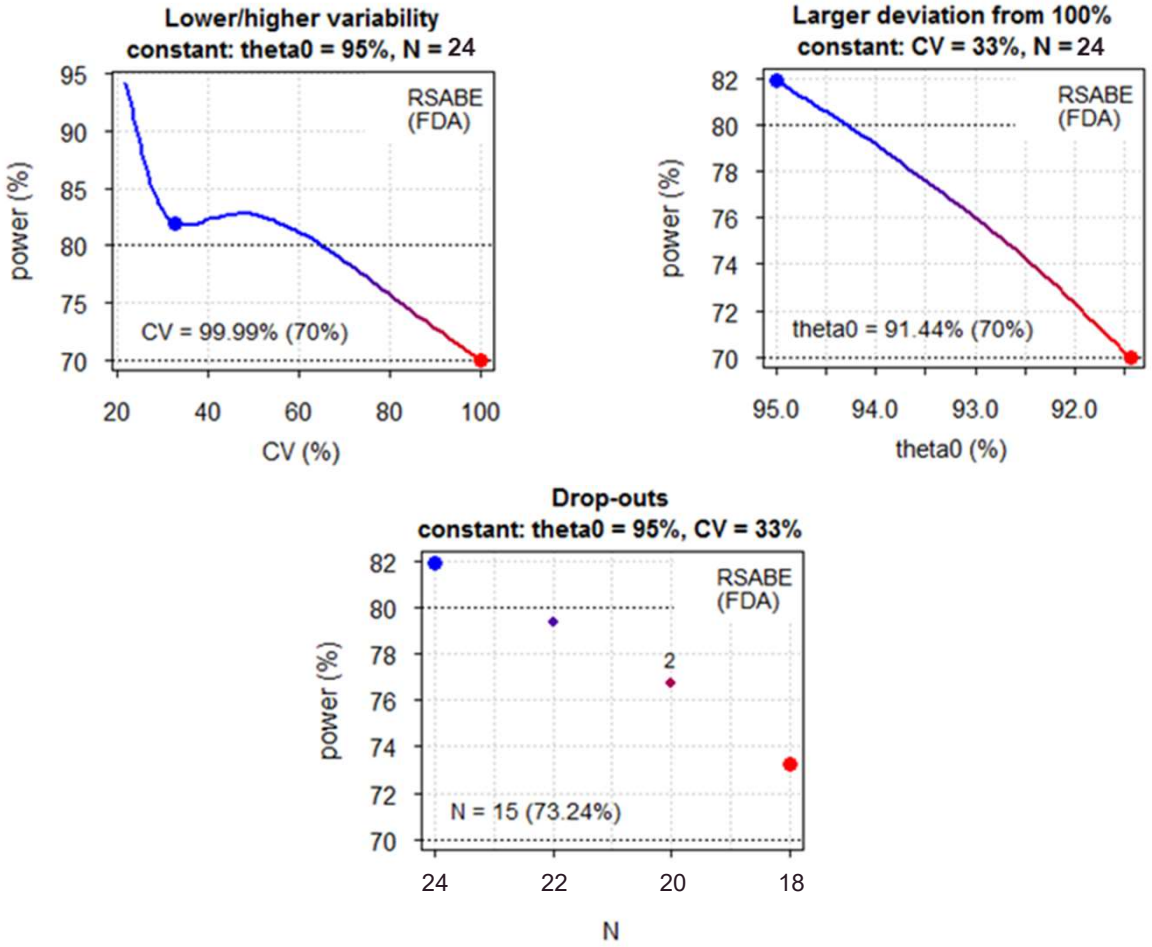
Intra-Subject CV and Study Power – Fasted State



- Study in 24 subjects (to achieve >80% probability of passing, using true GMR = 0.95 & ISCV = 33%)

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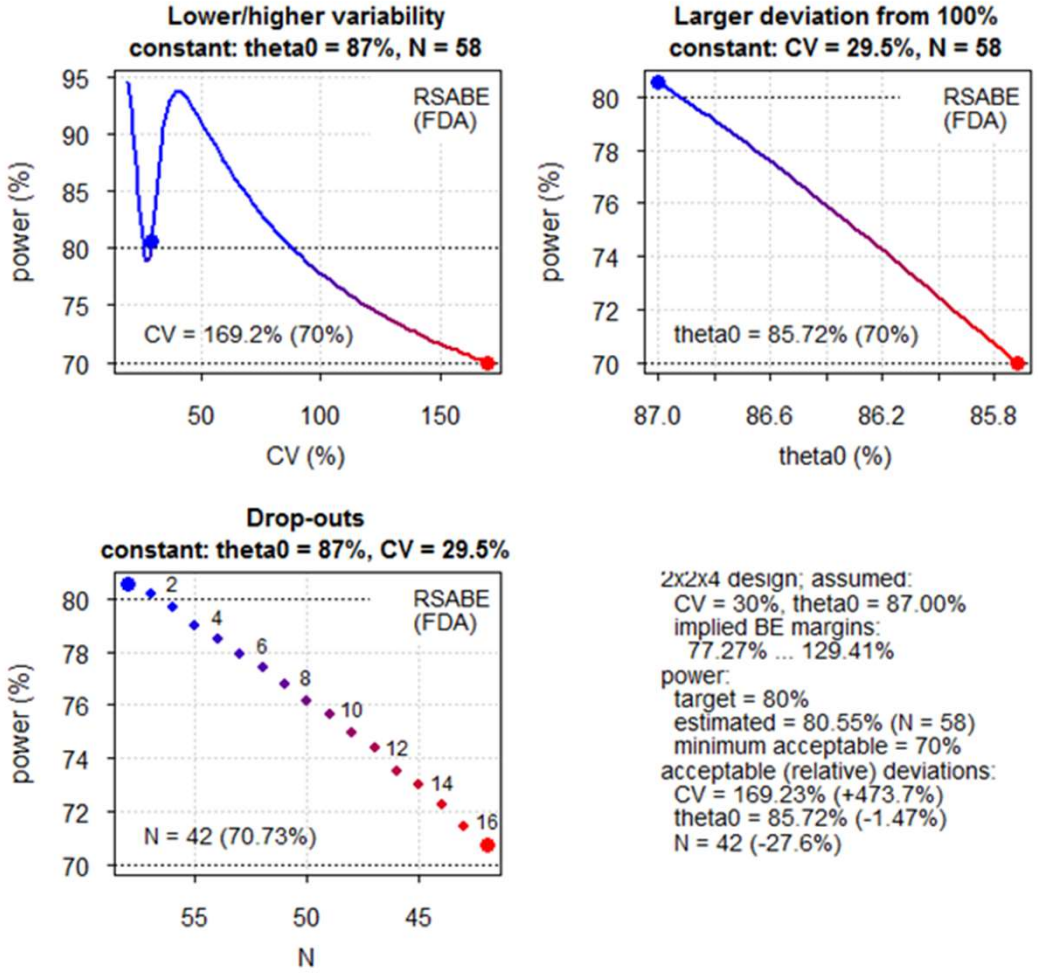
Intra-Subject CV and Study Power – Fed State



- Study in 58 subjects (to achieve >80% probability of passing, using true GMR = 0.87 & ISCV = 29.5%)

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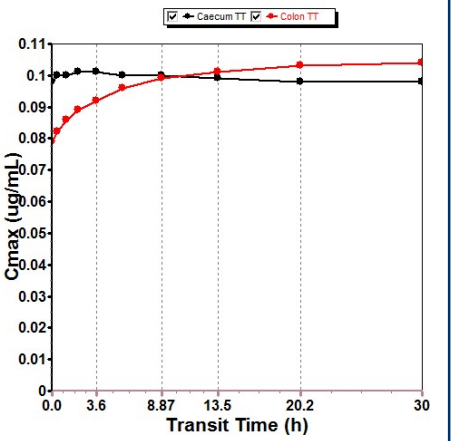
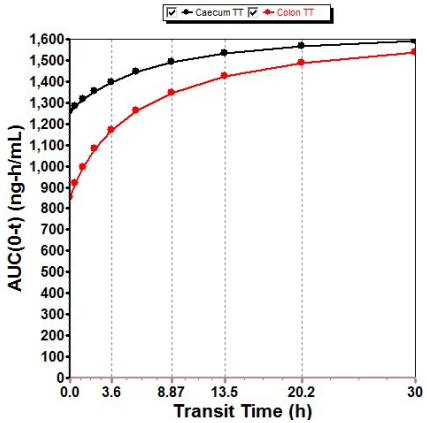
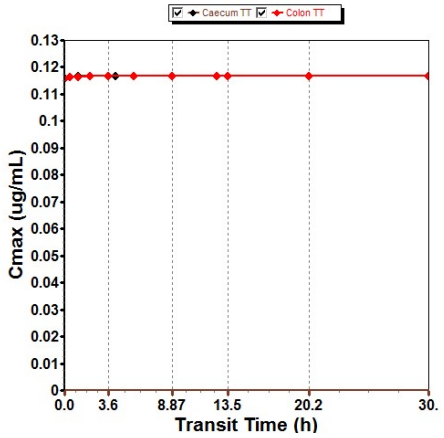
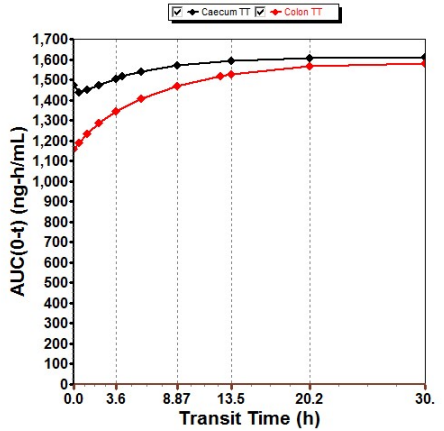
Effect of Lower Gut Transit Time on PK

Fasted		Fed	
Impact of Transit Time			
			

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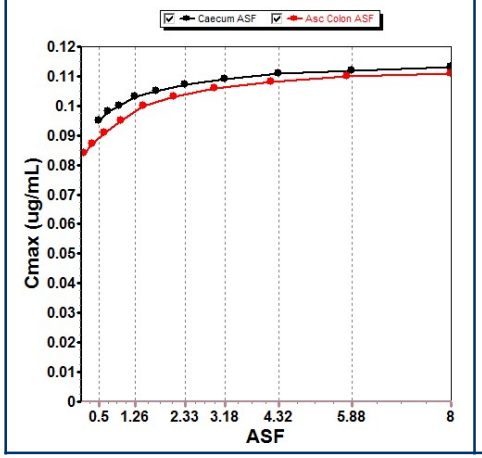
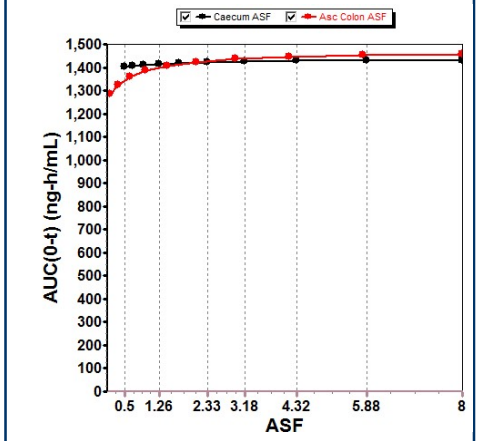
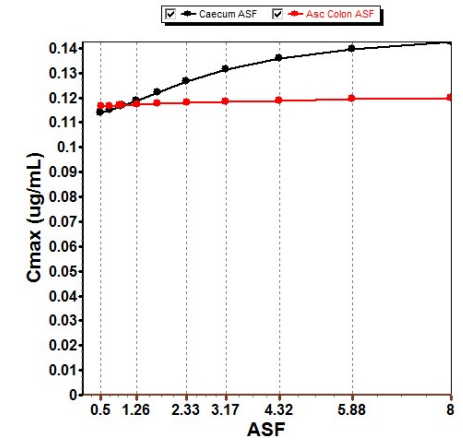
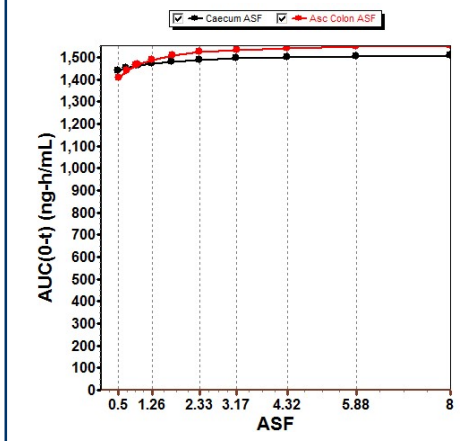
Effect of Lower Gut Absorption on PK

Fasted		Fed	
Impact of ASF			
			

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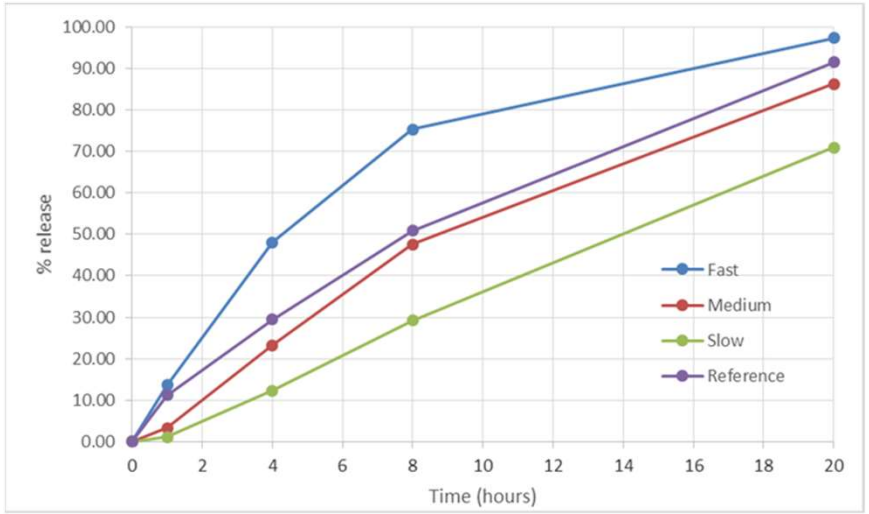
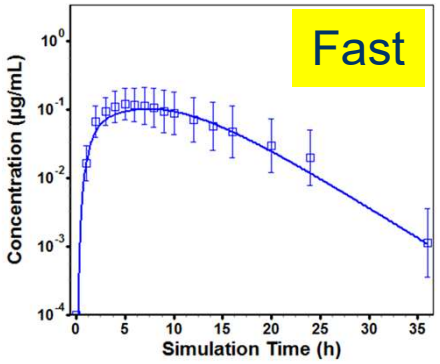
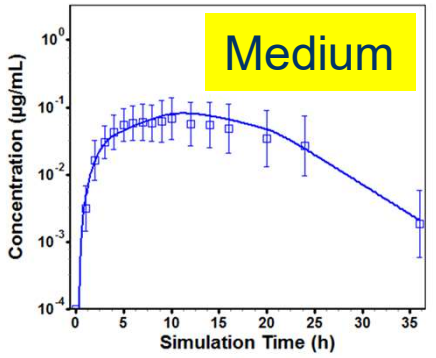
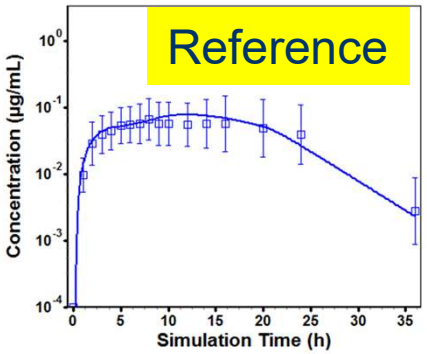
Single Simulations to Assess Model Performance

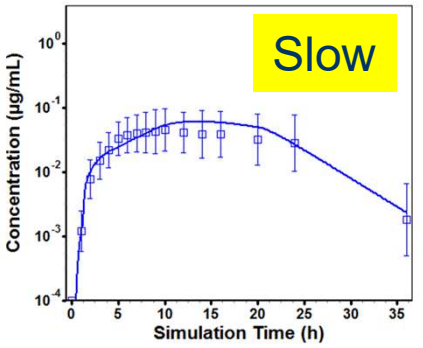
Fasted State











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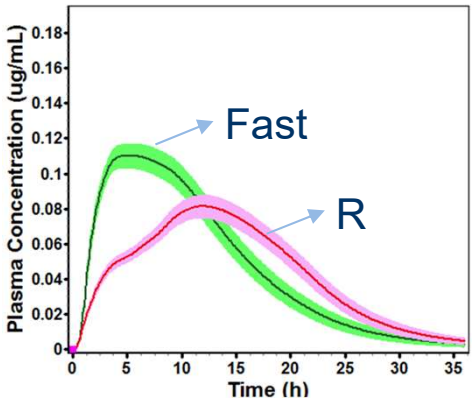
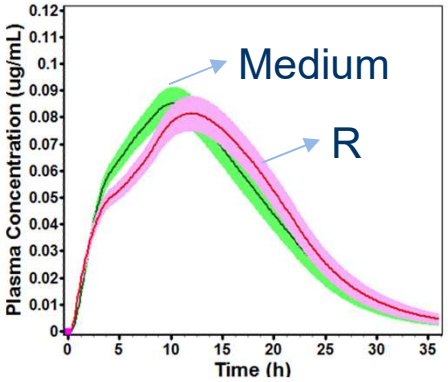
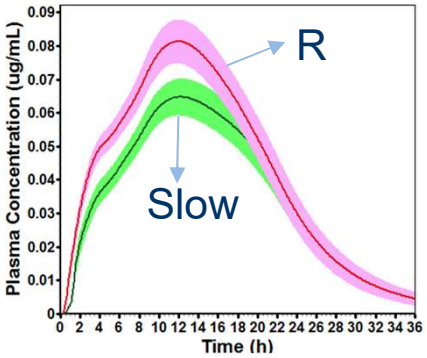
Population Simulations to Assess Fasted BE

- 10 population simulations were conducted in a cross-over manner with 24 subjects in each study
- CV for physiological parameters were constrained at 10%
- The GMR & 90%CI were calculated in Bioequivalence package in Phoenix







	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)
	Observed		Predicted	
Fast vs. R	1.11 (0.99-1.23)	1.83 (1.67-1.98)	1.09 (0.91-1.18)	1.54 (1.23-1.77)
Medium vs. R	0.86 (0.74-0.98)	1.02 (0.87-1.17)	0.95 (0.89-1.01)	1.10 (0.88-1.02)
Slow vs. R	0.75 (0.63-0.87)	0.75 (0.59-0.91)	0.84 (0.77-0.99)	0.84 (0.70-0.95)

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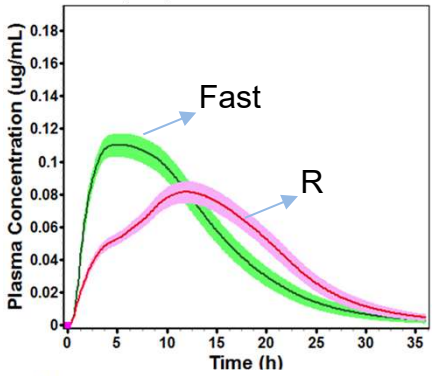
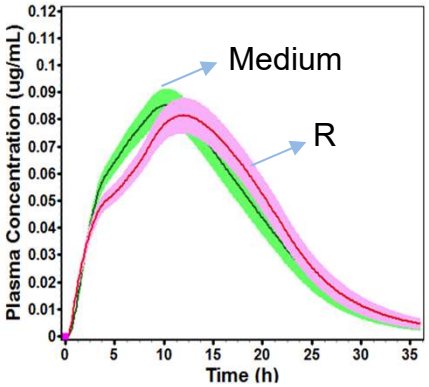
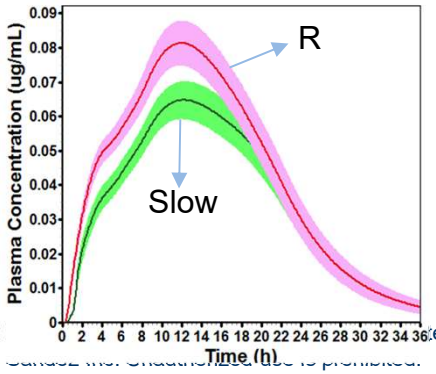
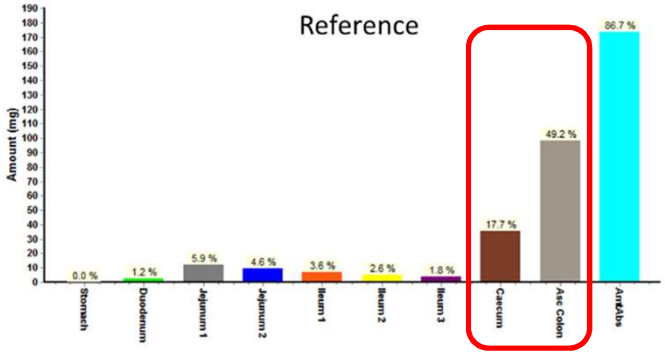
Population Simulations and Regional Absorption Predictions

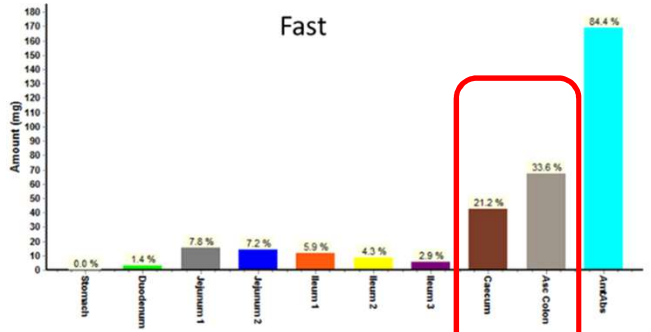
- 10 population simulations were conducted in a cross-over manner with 24 subjects in each study

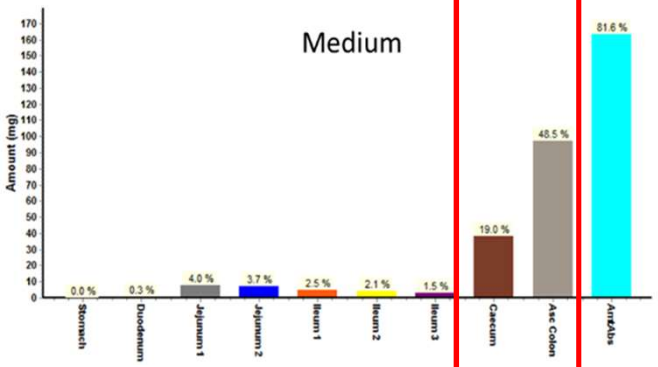


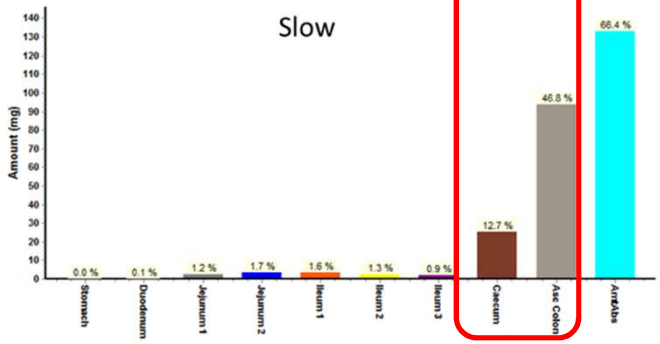












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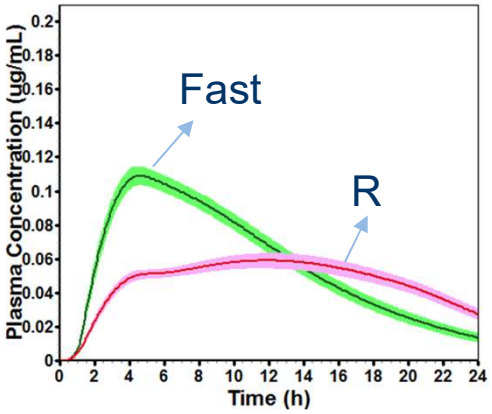
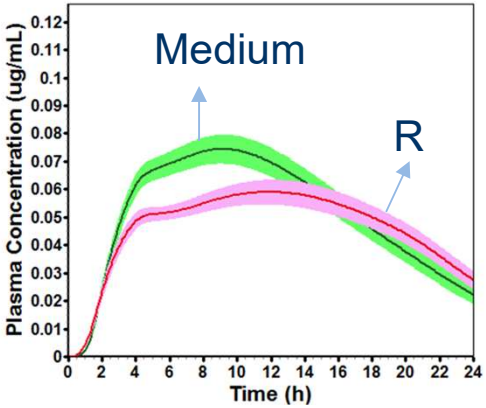
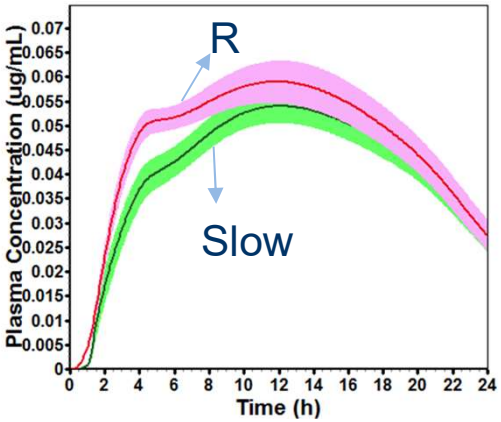
Population Simulations to Assess Fed BE

- 10 population simulations were conducted in a cross-over manner with 58 subjects in each study







	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)
	Observed		Predicted	
Fast vs. R	1.29 (1.18-1.39)	2.07 (1.88-2.27)	1.20 (1.01-1.27)	1.85 (1.71-2.01)
Medium vs. R	1.06 (0.95-1.17)	1.15 (0.96-1.35)	0.95 (0.89-1.19)	1.21 (1.05-1.41)
Slow vs. R	0.82 (0.70-0.92)	0.72 (0.52-0.91)	0.88 (0.71-1.01)	0.92 (0.81-1.05)

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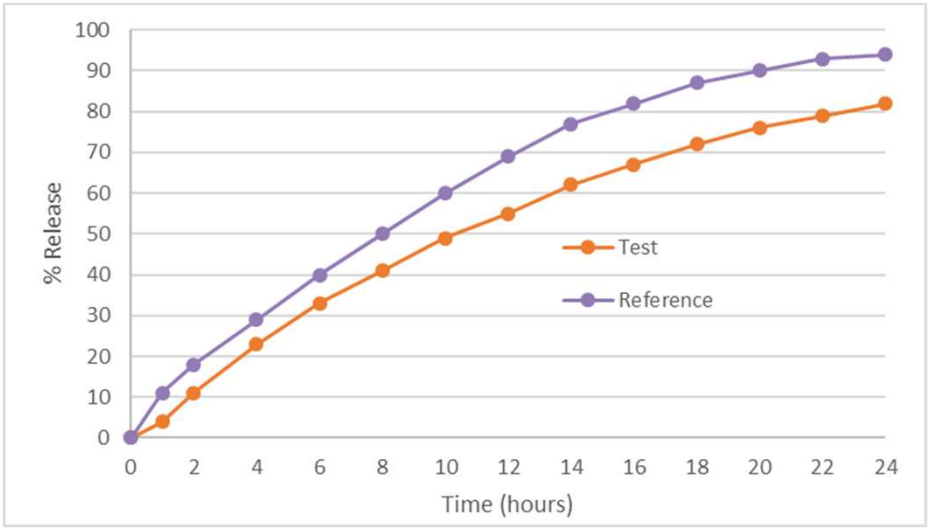
Projection of Pivotal BE Study in Fasted and Fed States

USP-2, pH 6.8



Observed BE Data

	AUC_{0-t} GMR (90% CI)	Cmax GMR (90% CI)
T/R *(fasted)*	0.89 (0.85-0.99)	0.90 (0.86-0.95)
T/R (*fed*)	1.00 (0.94-1.07)	0.99 (0.93-1.08)

Outcome of 10 Virtual Trials for Each Formulation in Fasted State

		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9	Trial 10
T/R	AUC										
	C_{max}										

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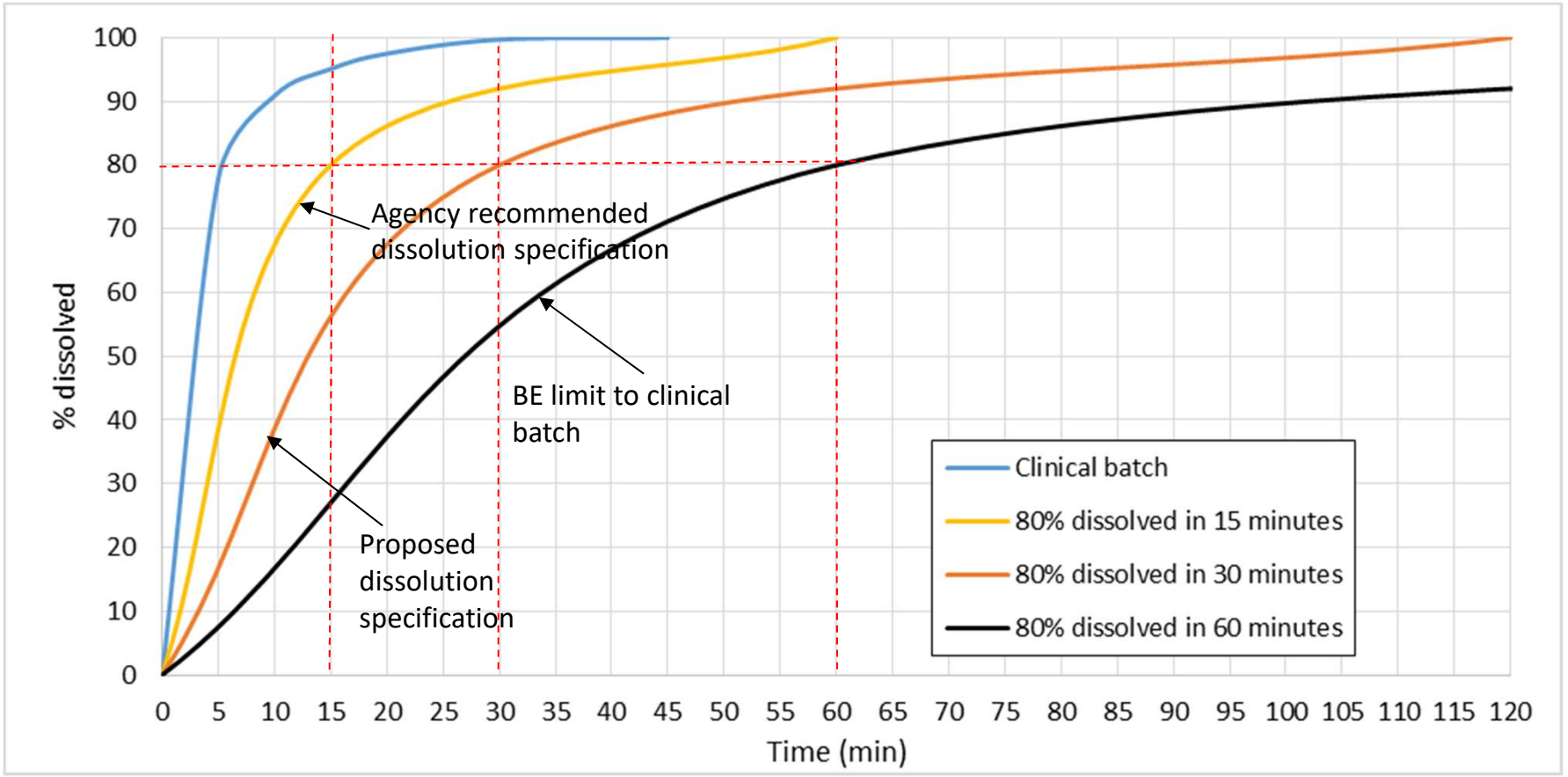
***Example 1*: Dissolution Specification Justification**



Mitra, Clin Pharmacol Ther. 105, 307-309 (2019)

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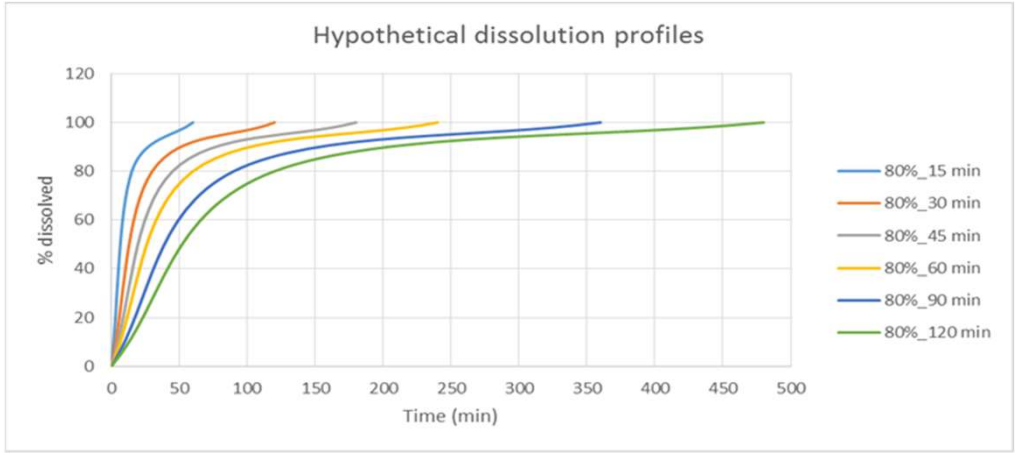
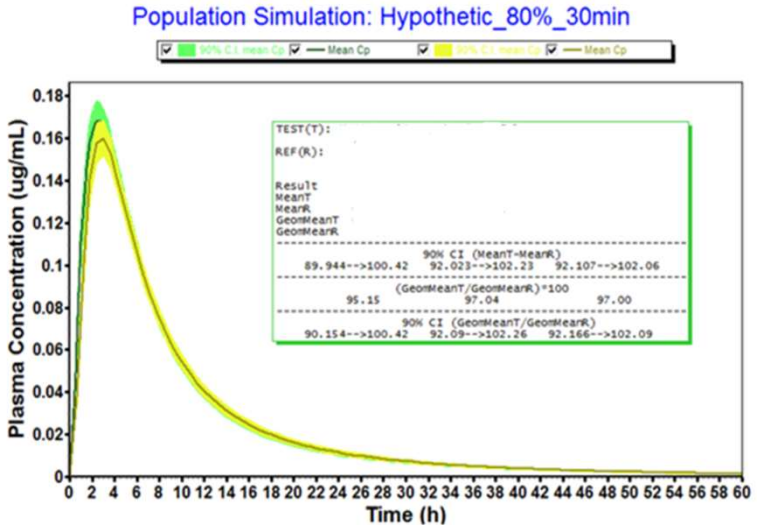
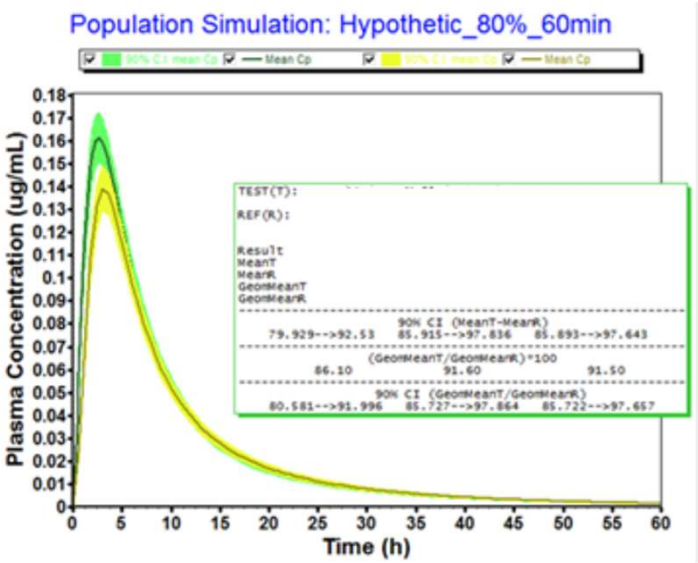
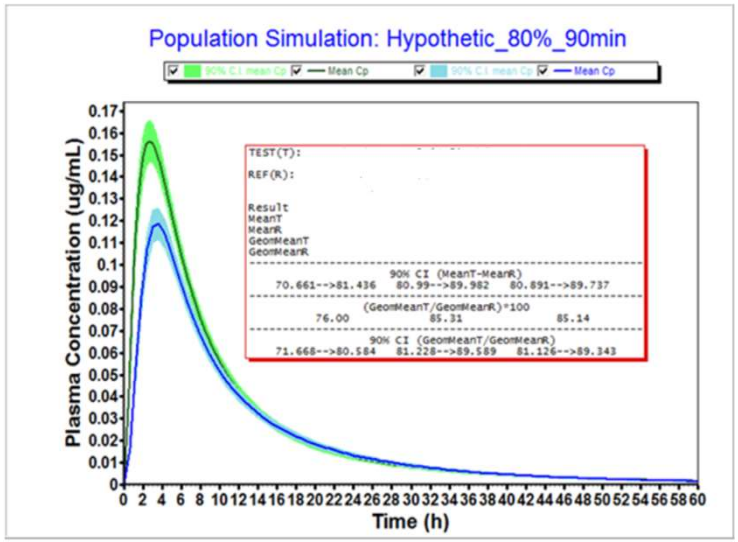
Effect of Dissolution on Bioequivalence to Clinical Batch









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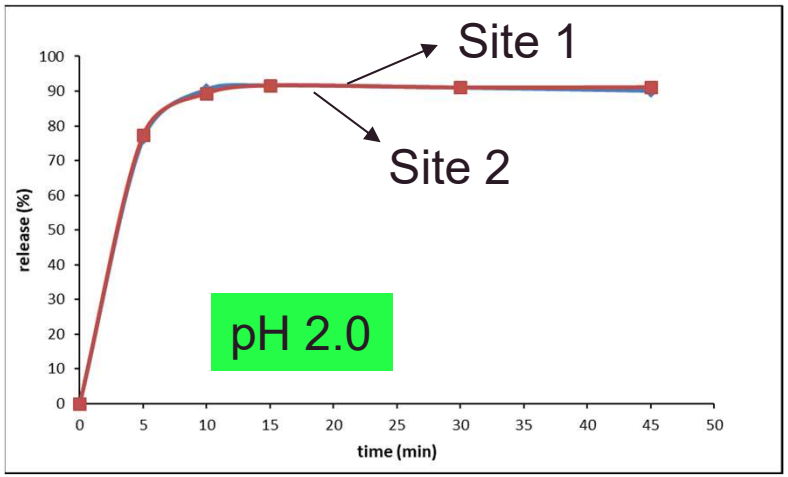
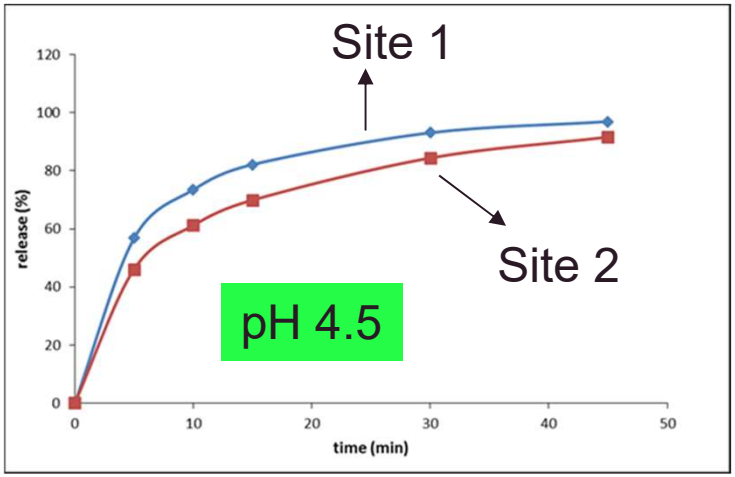
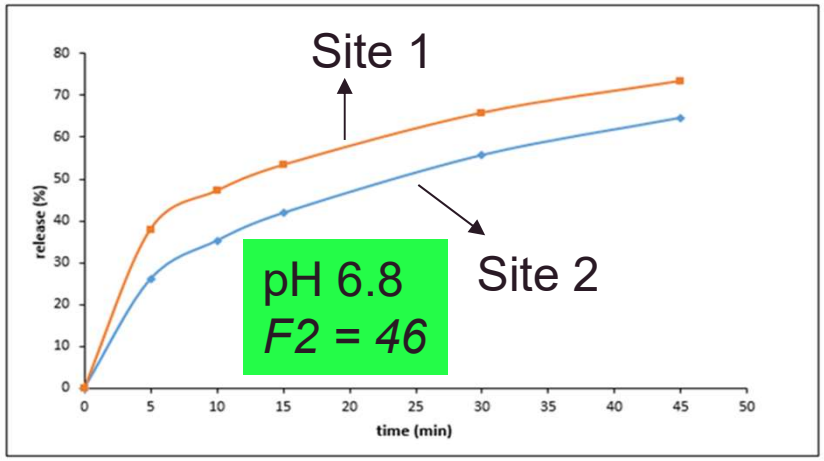
***Example 2*: Manufacturing Site Change**

BCS class 2 weak base







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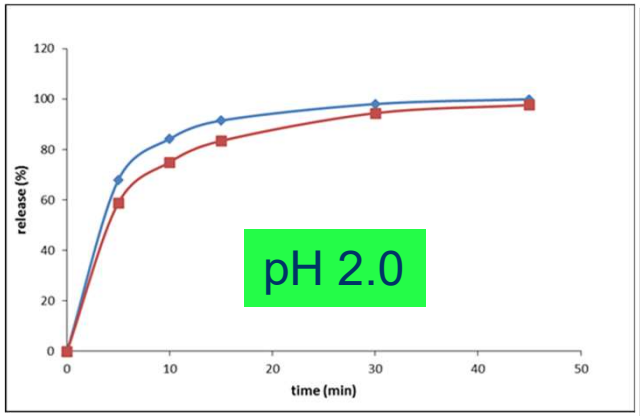
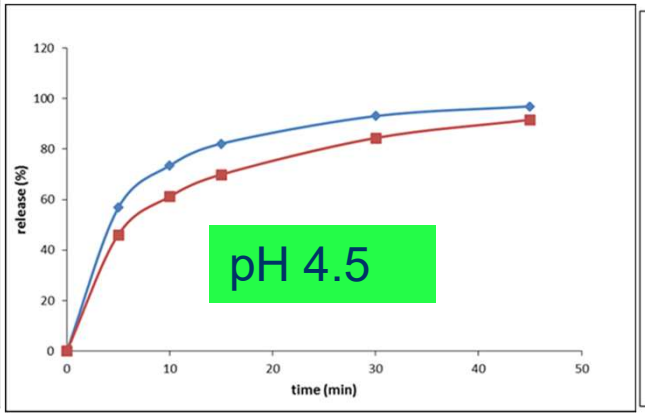
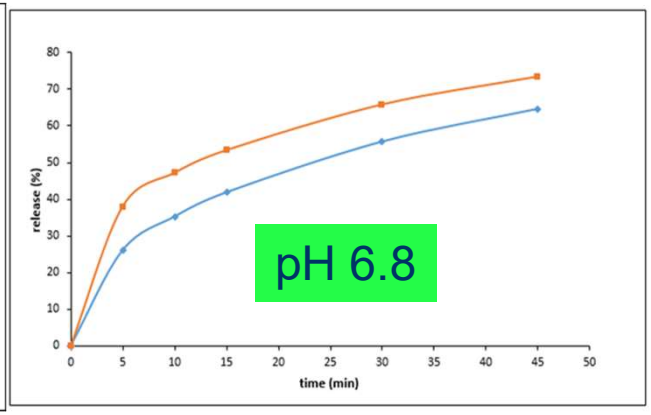
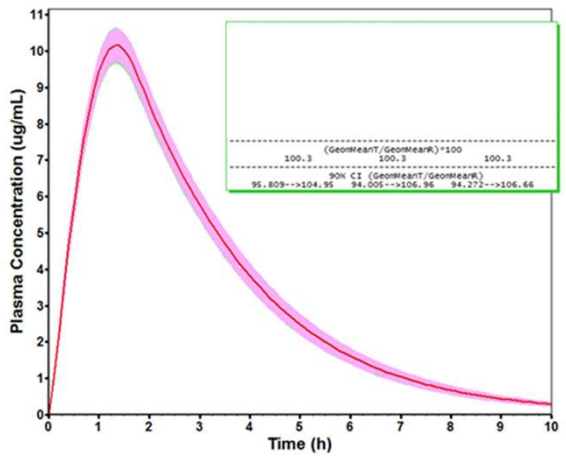
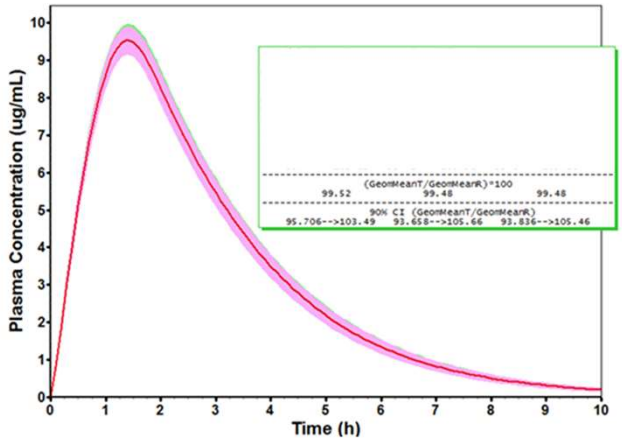
***Example 2*: Effect of dissolution differences on BE**

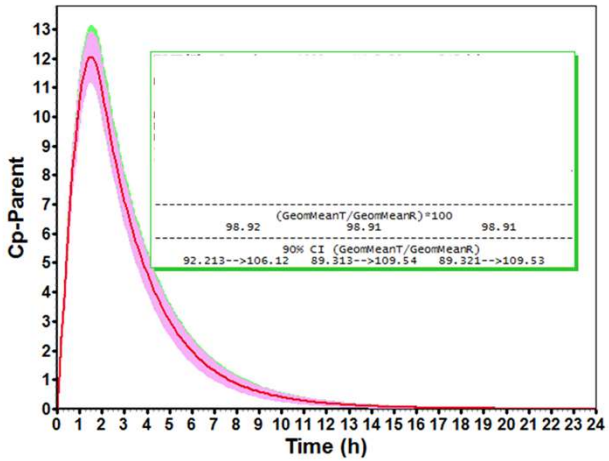












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Conclusion

- Current experiences highlight the increasing value of VBE applications in drug development
- Challenges remain -
  - Better estimation & incorporation of ISCV of physiological parameters
  - Regulatory acceptance of VBE e.g. in study waiver

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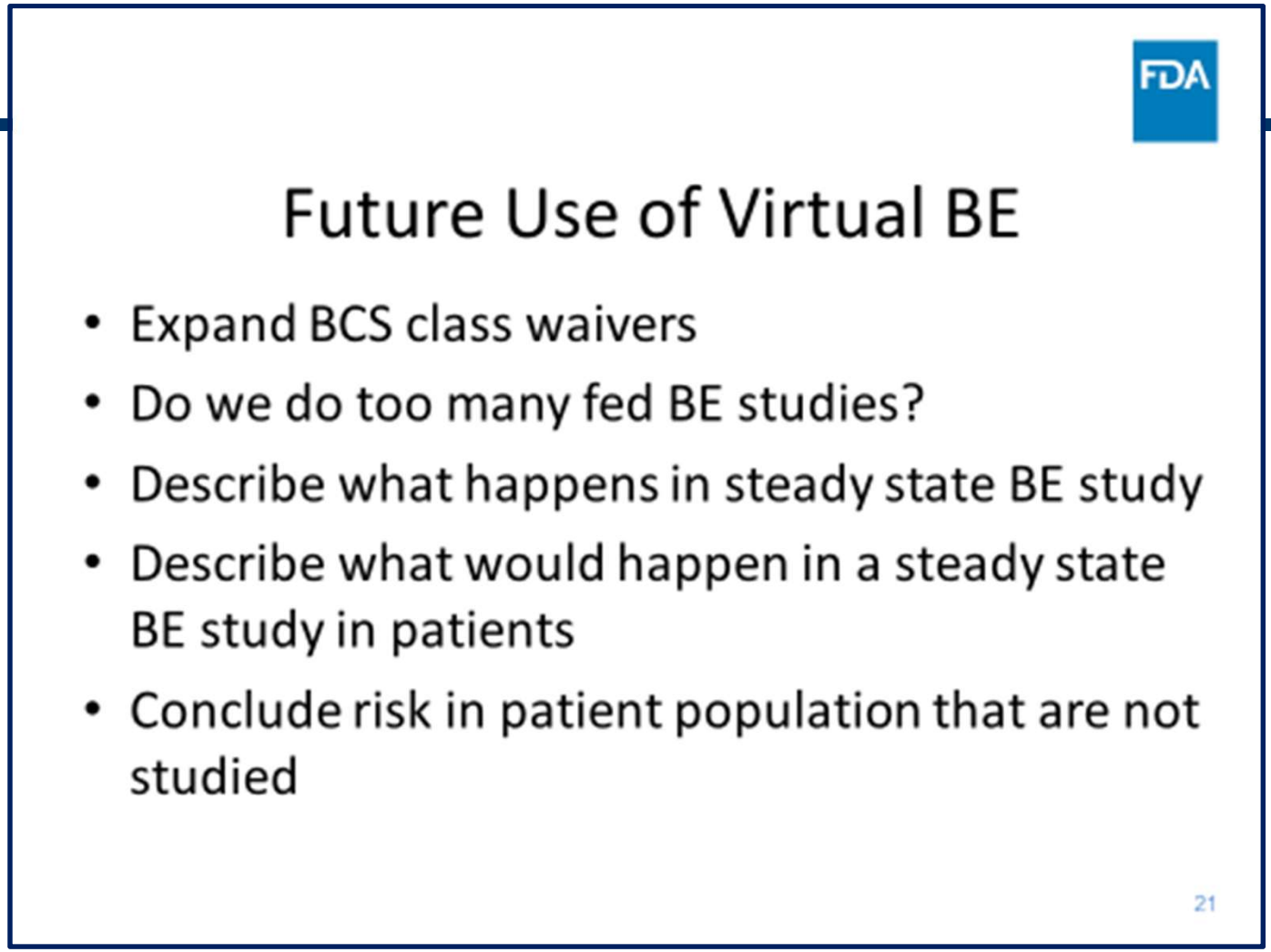

Slide courtesy of Rob Lionberger (FDA/CDER/OGD)

Presented at 2016 AAPS Annual Meeting *(Role of PBPK based virtual trials modeling in generic product development and regulation)*

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