FDA/M-CERSI, Best Scientific Practices Workshop; Latest Regulatory and Industry Perspectives Tue 29th–Thur 31st August 2023
University of Maryland; Shady Grove (Rockville, MD)

Hot Topic H: Considerations for Model Application

VBE Trials *vs* Single Representative Modeling

Dealing with Within- and Between-Subjects Variability (WSV & BSV) and Parameter Uncertainty

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Declaration of Conflict of Interest

As the Director of CAPKR (Centre for Applied Pharmacokinetics Research my research is sponsored by a group of pharmaceutical companies (currently AbbVie, Amgen, Eli Lily, EMD Serono, Genentech, GSK, J&J, Roche, Servier, Takeda) in addition to grants from non-for-profit organizations, governments and research councils.

As the Chief Scientific Officer and SVP of R&D at Certara, I have been involved in overseeing the development of software tools by Certara Inc which are used by a large group of pharmaceutical companies during drug discovery and development; particularly in the area of physiologically-based pharmacokinetics (PBPK) and quantitative systems pharmacology (QSP) and toxicology (QST).

Disclaimer

This presentation is prepared in my *personal capacity* as a scientist engaged with clinical pharmacology and pharmaceutical science for over 30 years.
The opinions expressed herein are my own and do not reflect the views, policies, and strategies of any of the organisations I am affiliated with.

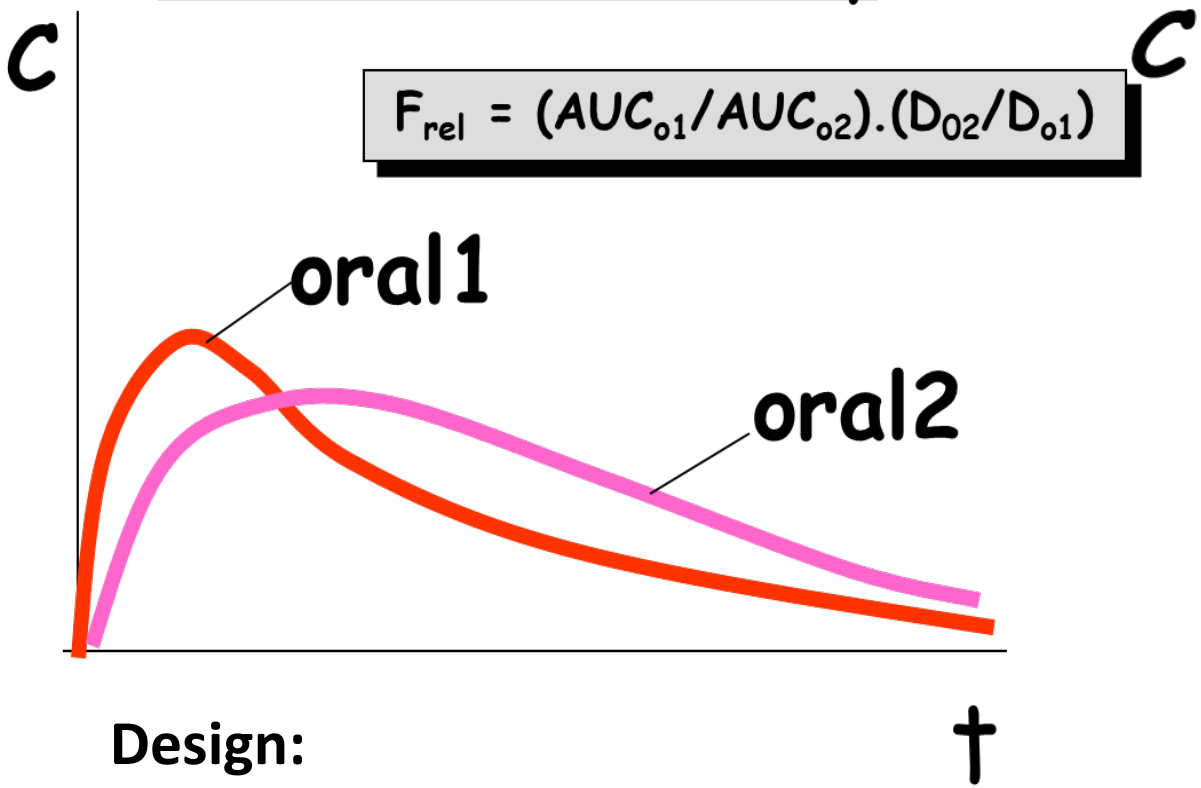
Two formulations giving rise to

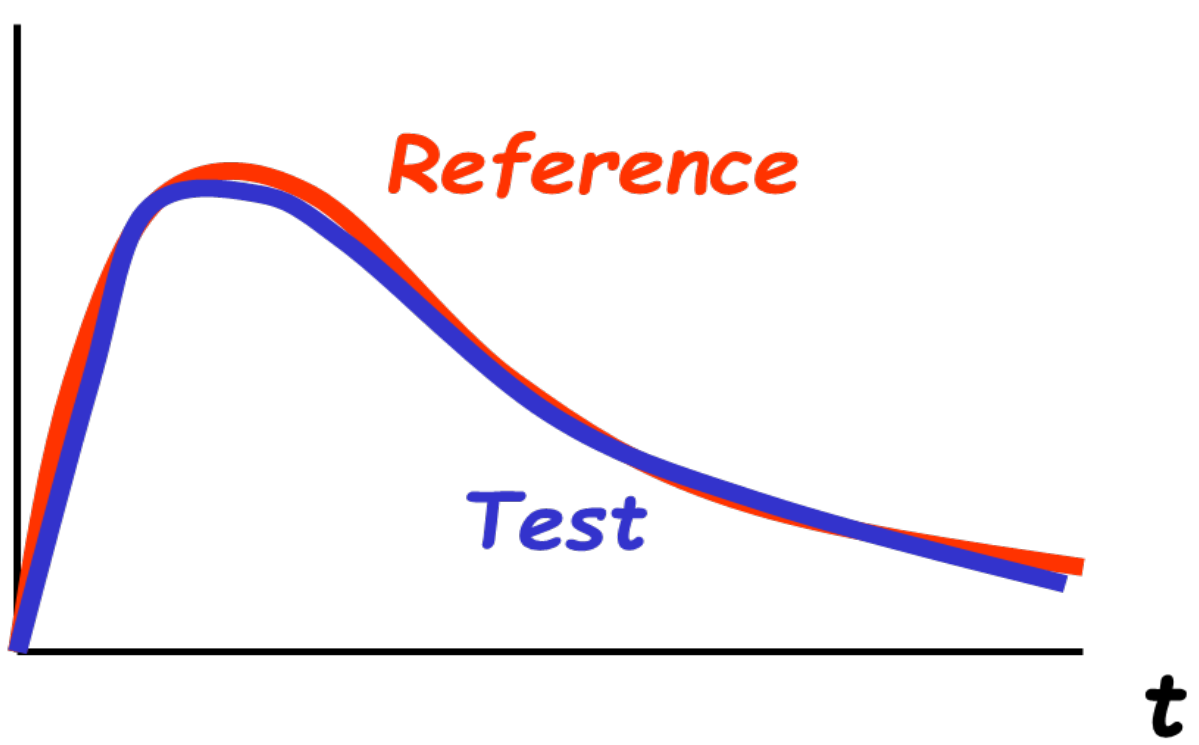
essentially similar drug concentration-time profiles

provide equivalent therapeutic effect:

Relative Bioavailability

$$F_{rel} = (AUC_{o1}/AUC_{o2}).(D_{02}/D_{o1})$$





Design:

(1) Mostly R-T Cross-Over;
(2) Parallel with larger number if wash-out is too long;
(3) RTR and RTRT if WSV is too high

Proof of Concept in Assignment of Within-Subject Variability During Virtual Bioequivalence Studies: Propagation of Intra-Subject Variation in Gastrointestinal Physiology Using Physiologically Based Pharmacokinetic Modeling

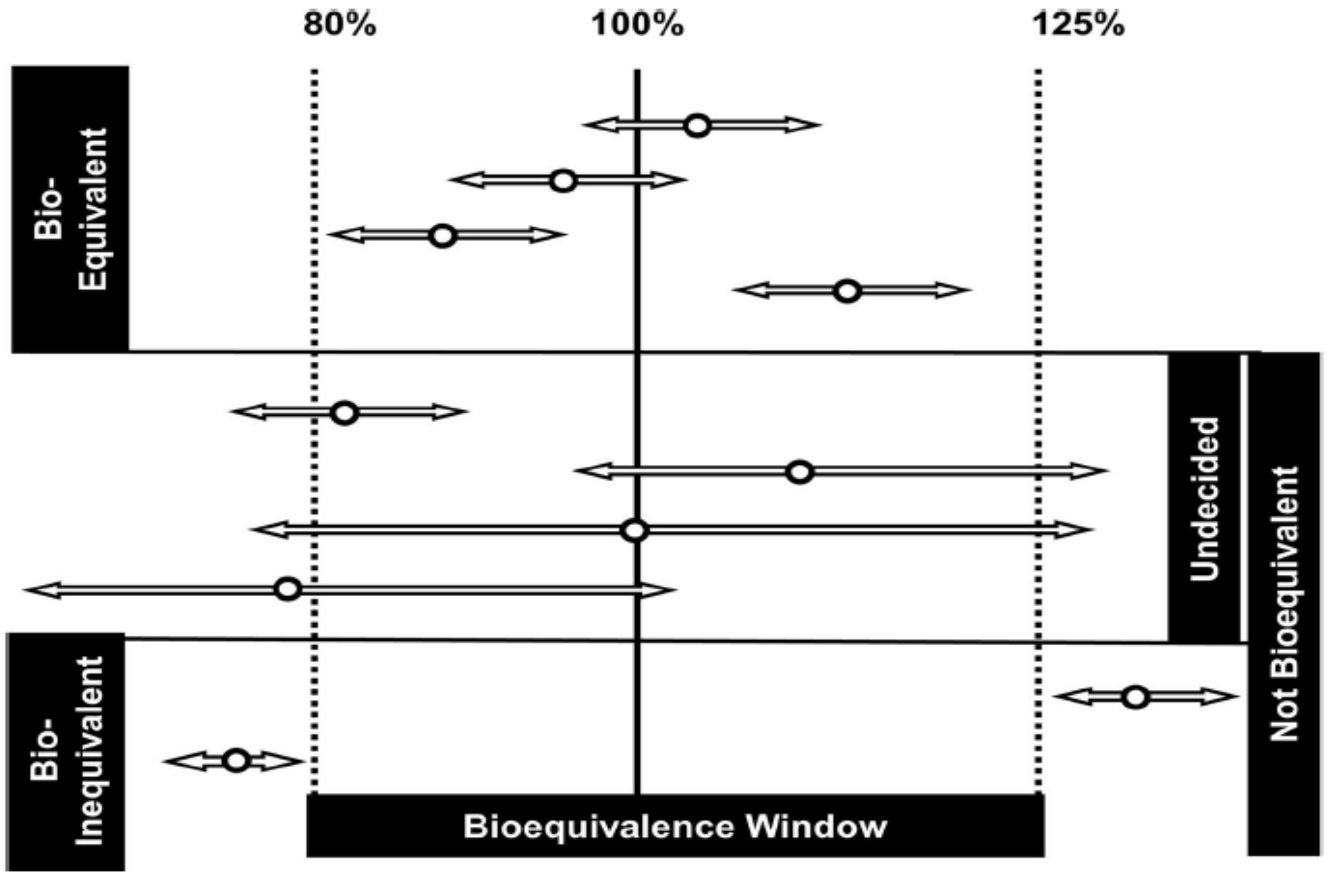
Margareta Bego, Nikunjkumar Patel, Rodrigo Cristofoletti, Amin Rostami-Hodjegan
AAPS J. 2022 Jan 5;24(1):21

An ESSENTIAL READ for Anyone Conducting VBE

Clinical BE Studies have NEVER been based on central tendency ALONE!

This is for a VERY GOOD REASON!

(see the next slide)

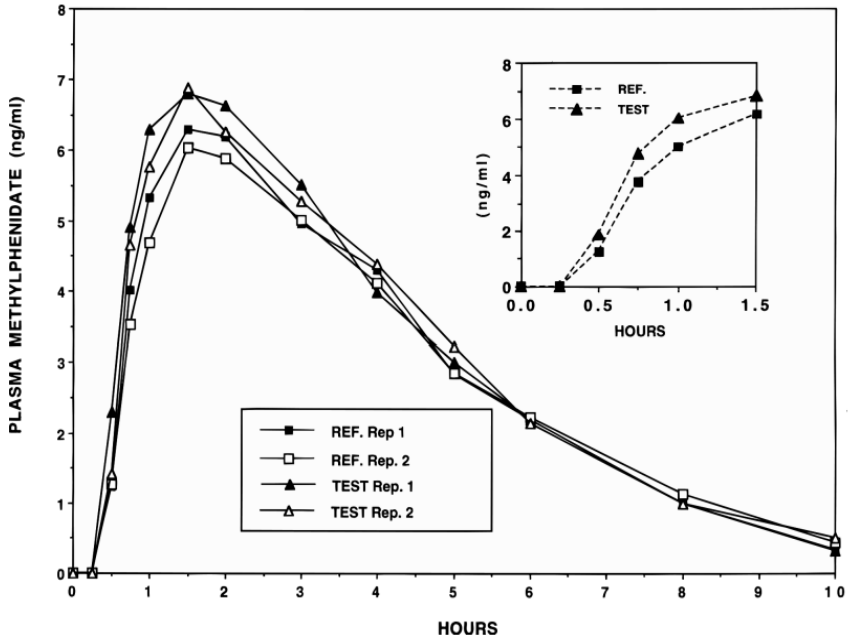


Evidence for Formulation-Dependent WSV

Methyphenidate: Insight from RTRT Design

Comparison	Mean (ng × hr/ml)	Percent	Confidence limits Ln cmax
REF. 1, REF. 2	7.01, 6.70	96–105%[a]	84–119%
TEST 1, TEST 2	7.72, 7.45	97–104%[b]	76–131%
TEST 1, REF. 1	7.72, 7.01	110%[c]	103–123%
TEST 1, REF. 2	7.72, 6.70	115%[c]	84–117%
TEST 2, REF. 1	7.45, 7.01	106%[c]	106–138%
TEST 2, REF. 2	7.45, 6.70	111%[c]	93–123%
Mean TEST, REF.	7.58, 6.85	111%[c]	99–121%

[a] (Ref. 1/Ref. 2) and (Ref. 2/Ref. 1).
[b] (Test 1/Test 2) and (Test 2/Test 1).
[c] (TEST/REF.).



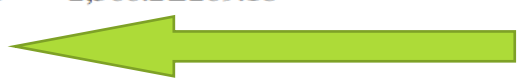
- Faster Dissolution & Absorption of T *vs* R
- T *vs* T more variable than R *vs* R
- On Average T(1&2) *vs* R(1&2) ➔ BE
- On Individual Trial Basis of T *vs* R ➔ Not-BE

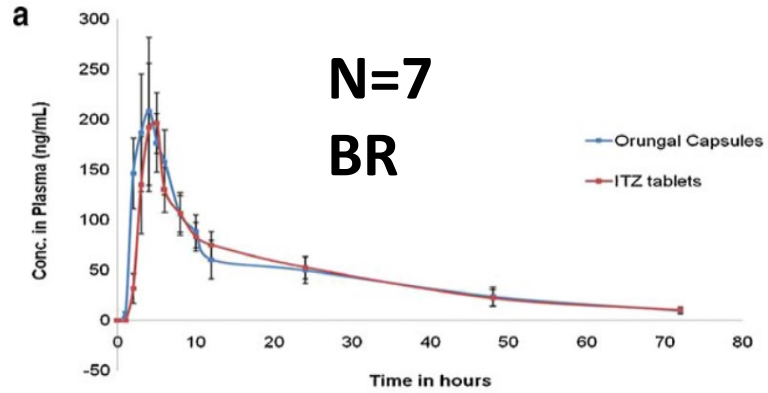
Meyer et al. 2000

Misinterpreting the Effects of Formulation-Dependent WSV

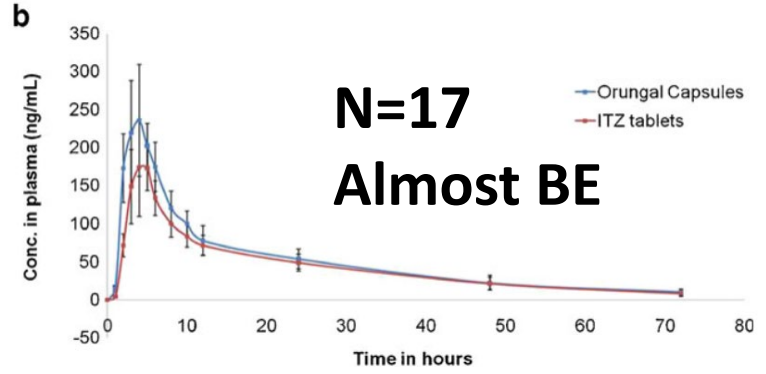
Itraconazole

Parameter	Test	Reference
Number of volunteers	7	7
C_{max} (ng/ml)	150.8±49.34	171.72±68.21
AUC last (hng/ml)	2,236.9±389.58	2,179.3±477.29
AUC infinity (hng/ml)	2,553.4±425.16	2,366.2±269.18
CI 90 (AUC last)	93.56–112.61	
CI 90 (AUC infinity)	95.21–122.31	
Ratio (% ref) AUC last	102.65	
Ratio (% ref) AUC ∞	107.91	

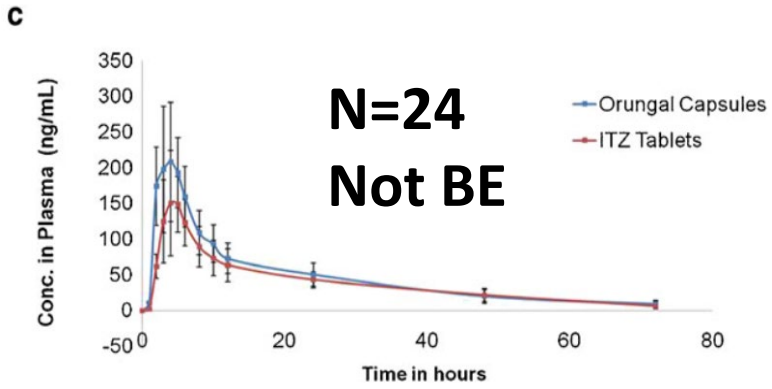


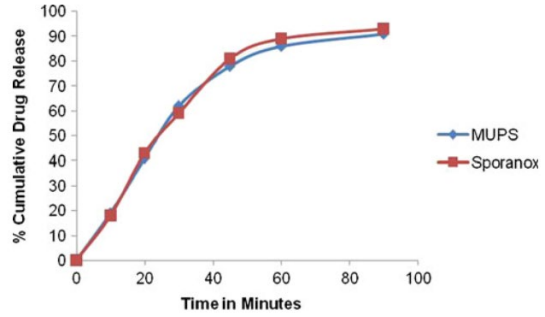


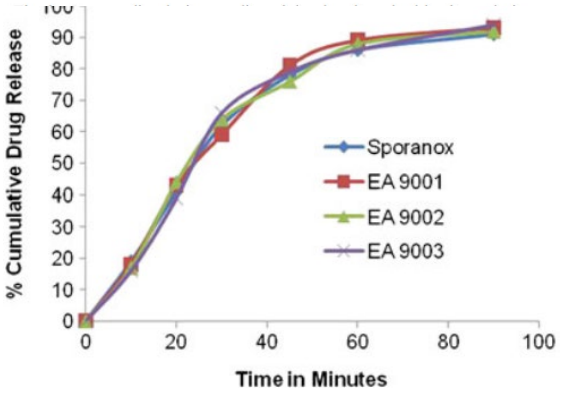
Parameter	Test	Reference
Number of volunteers	17	17
C_{max} (ng/ml)	192.2±93.17	219.55±81.56
AUC last (hng/ml)	2,899.3±672.37	3,005.1±589.28
AUC infinity (hng/ml)	3,179.7±659.78	3,331.8±712.94
CI 90 (AUC last)	81.9–113.66	
CI 90 (AUC infinity)	79.57–114.46	
Ratio (% ref) AUC last	96.48	
Ratio (% ref) AUC ∞	95.43	



Parameter	Test	Reference
Number of volunteers	24	24
C_{max} (ng/ml)	181.98±99.47	229.37±86.46
AUC last (hng/ml)	2,684.5±789.65	3,196.2±857.86
AUC infinity (hng/ml)	2,949.9±643.87	3,525.7±769.96
CI 90 (AUC last)	70.7–99.78	
CI 90 (AUC infinity)	70.22–99.70	
Ratio (% ref) AUC last	83.99	
Ratio (% ref) AUC ∞	83.67	





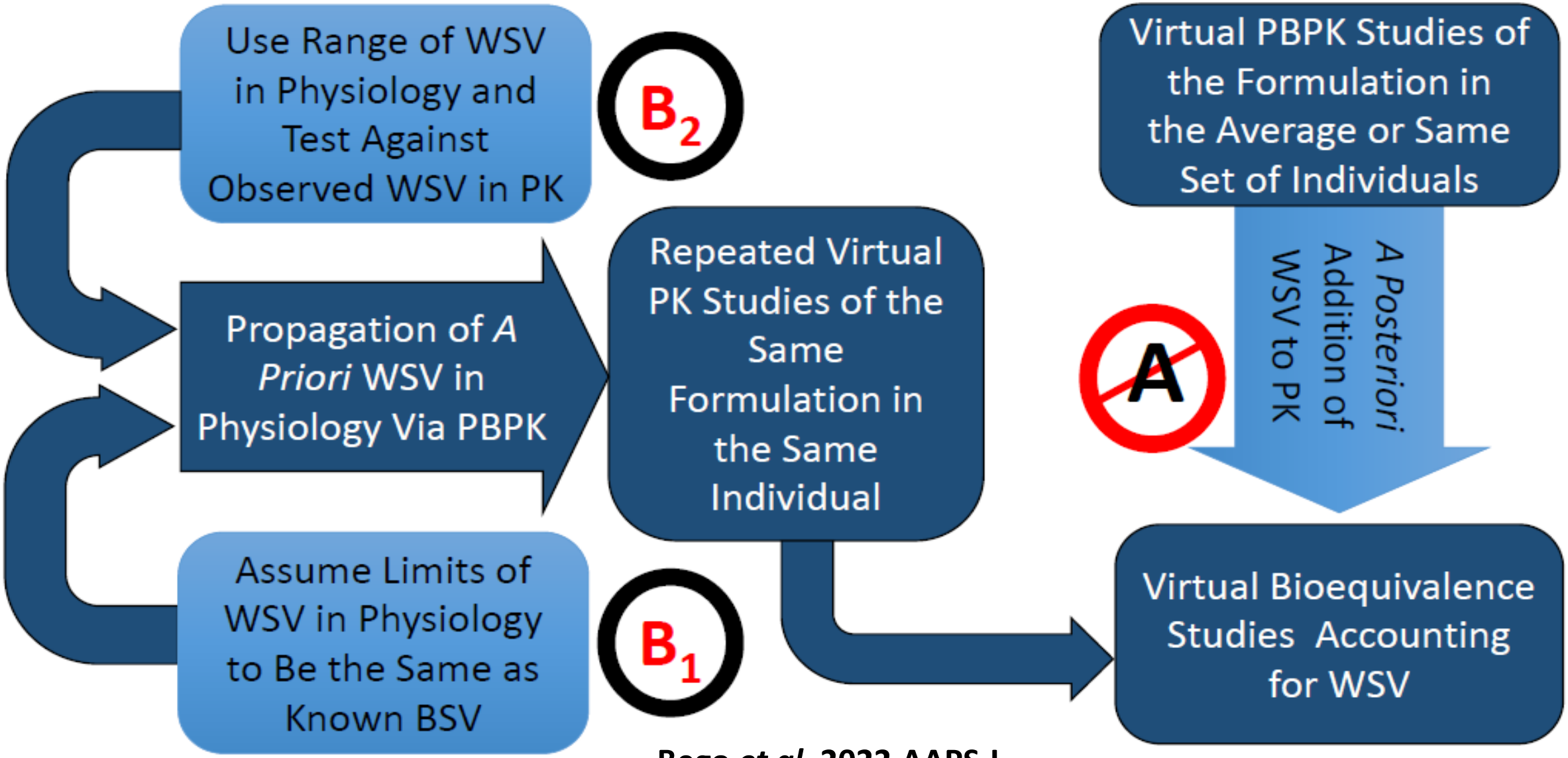


MUPS: Multi-Unit Particulate Systems

EA n: Scaled Up Batches of MUPS

Swaminathan et al. 2013

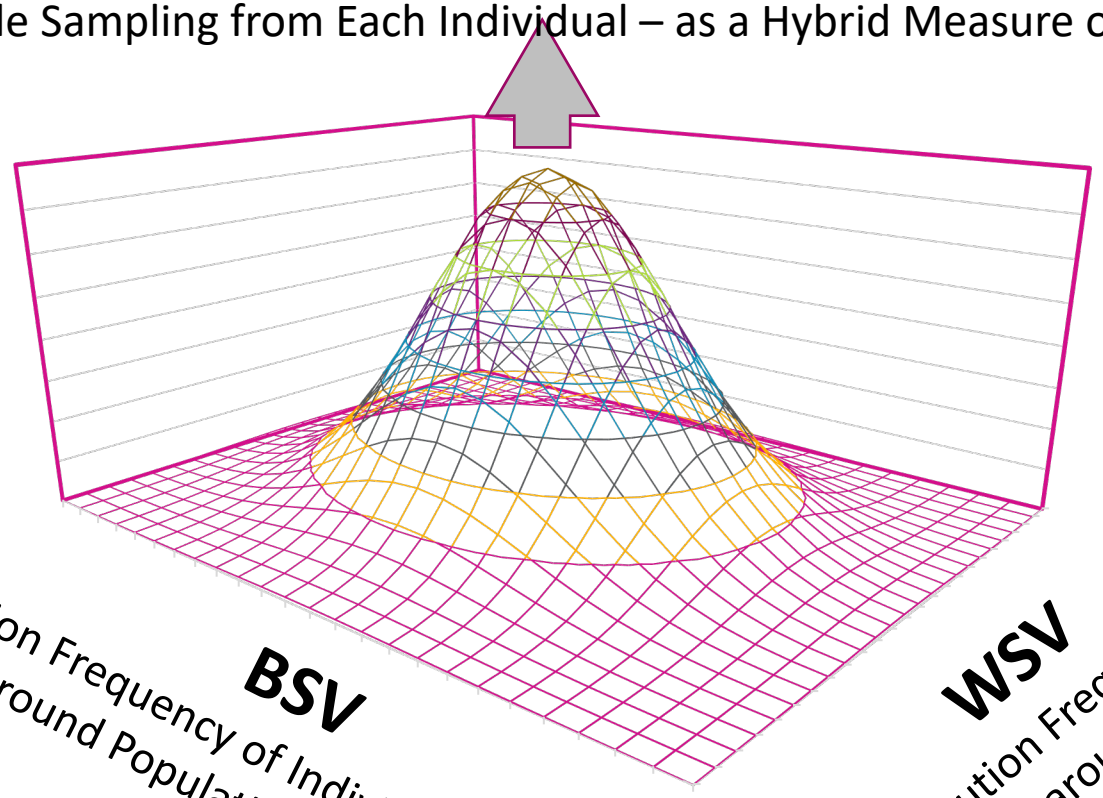
Right & Wrong of Accounting for WSV when Conducting VBE

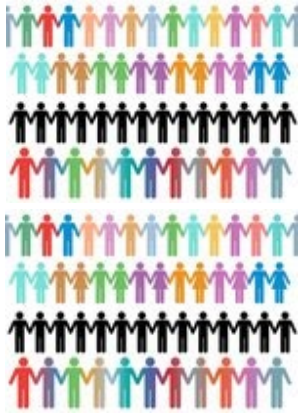


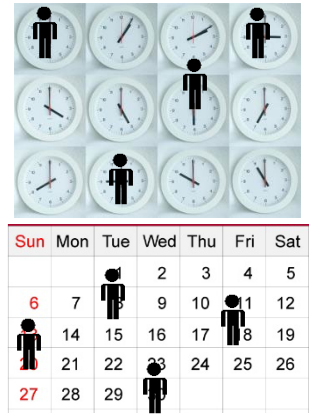
Bego *et al.* 2022,AAPS J

Apparent BSV

(Under Single Sampling from Each Individual – as a Hybrid Measure of BSV & WSV)







BSV

Distribution Frequency of Individual Mean Values Around Population Mean Value

WSV

Distribution Frequency of Individual Values around Their Own Mean

True BSV

(based on Based on Mean Values of Individuals)

WSV

(Under Repeat Sampling from an Individual)

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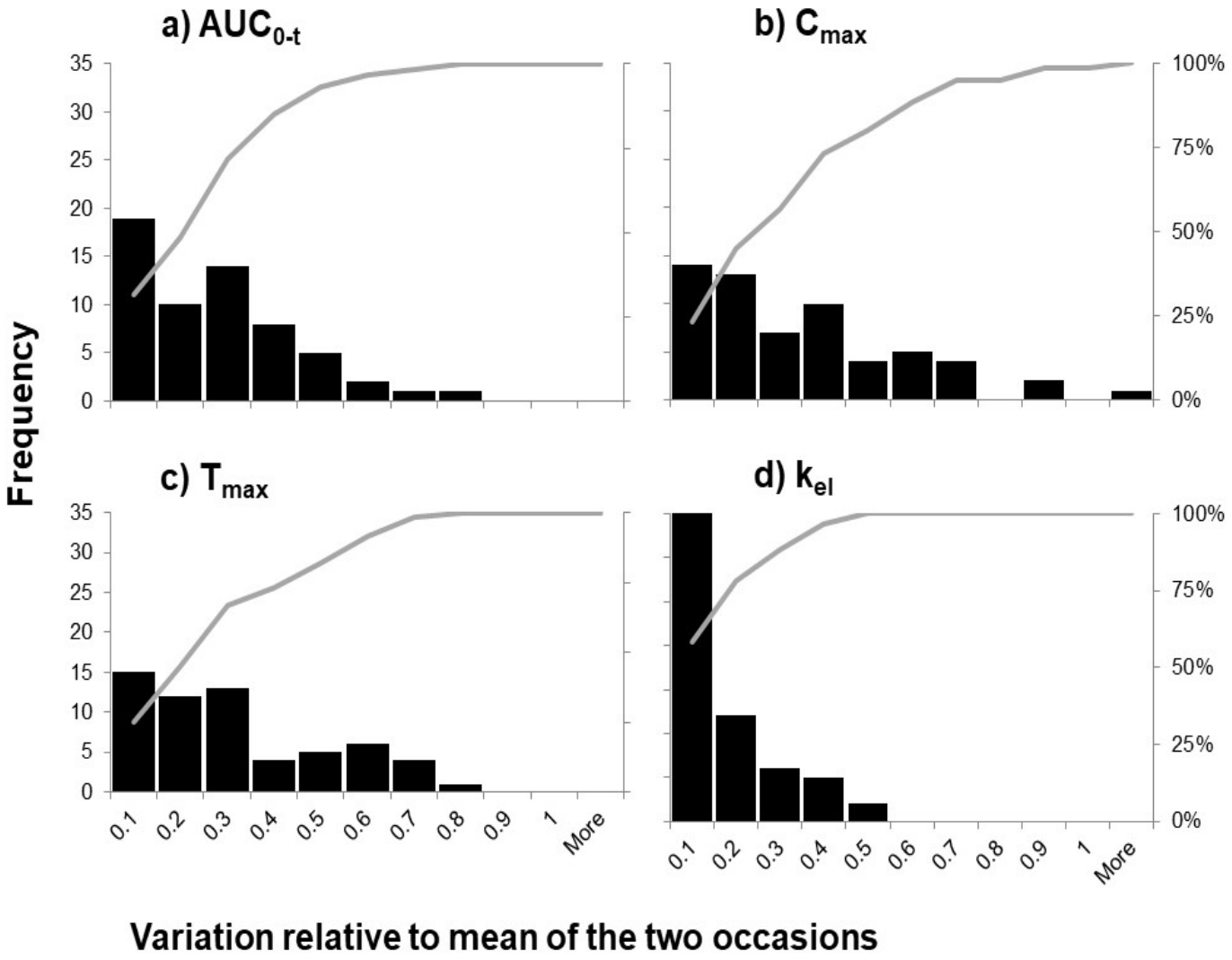
Availability of Measured WSV in Physiology in GI Tract: An Issue!

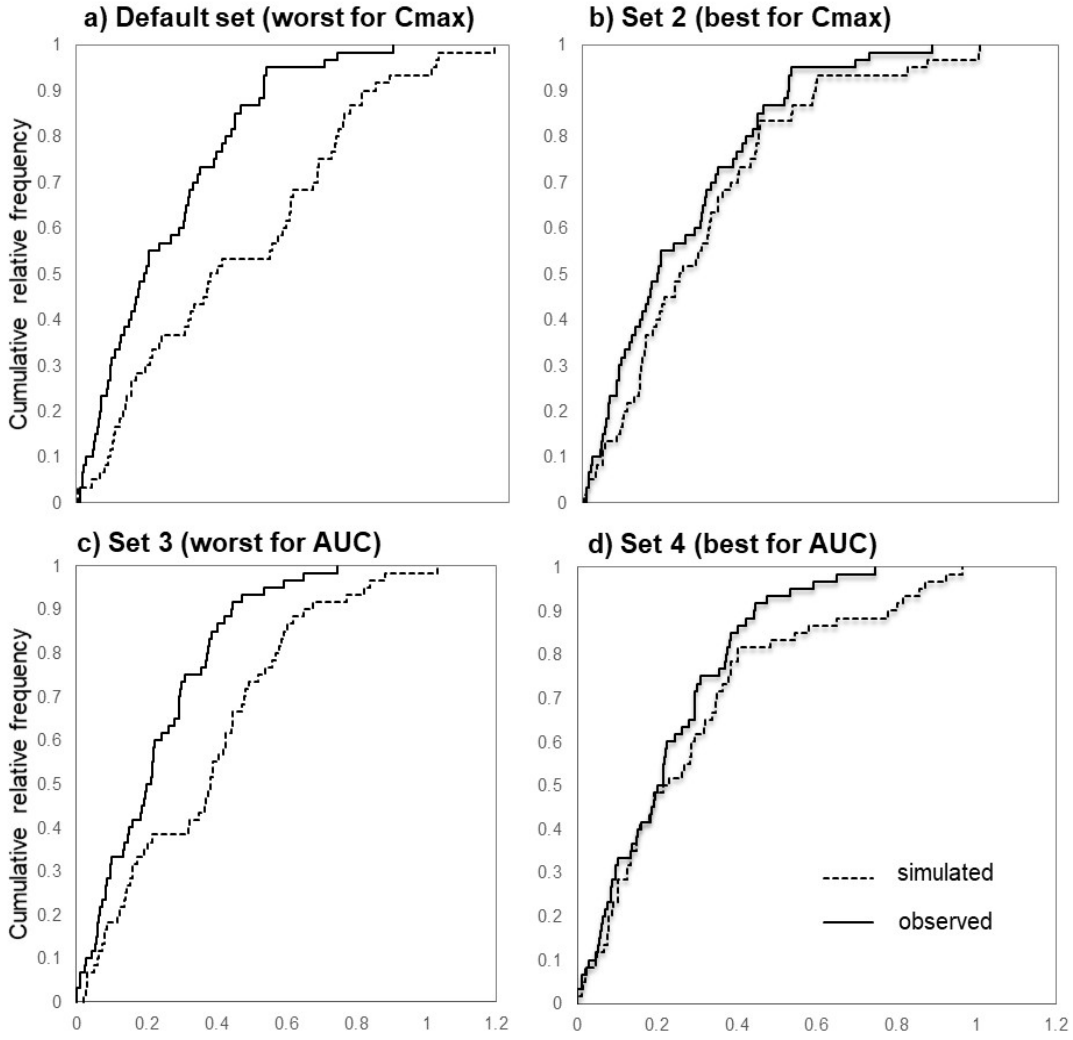
Table 2 Different sets of WSV in GI physiology investigated

Physiological Parameters - WSV CV%	Default	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9	Set 10	Set 11	Set 12	Set 13	Set 14
Gastric MRT(h)	38	19	19	19	25	30	25	25	30	25	19	38	38	38	19
Small Intestine MRT (h)	30	15	15	15	10	10	10	20	15	10	15	15	15	30	15
Colon MRT (h)	30	30	30	30	30	20	20	30	30	30	30	30	30	30	30
Duodenum pH Fasted	16	16	16	8	16	8	10	16	10	16	16	16	16	16	Dy
Duodenum Bile Salt Conc Fasted	97	97	49	97	70	97	70	49	49	49	49	97	97	97	49
Jejunum I pH Fasted	13	13	13	7	13	7	10	13	5	13	13	13	13	13	Dy
Jejunum I Bile Salt Conc Fasted	100	100	50	100	70	100	70	50	50	50	50	100	100	100	50
Jejunum II pH Fasted	11	11	11	6	11	6	10	11	5	11	11	11	11	11	Dy
Jejunum II Bile Salt Conc Fasted	42	42	21	42	30	30	30	21	21	21	21	21	42	21	21

CV% differing from the default (BSV) value are highlighted blue. CV% for volume of water administered was set to 1%, initial volume of stomach fluid at 30%, stomach pH at 38% and drug clearance to 5% in all sets except Set 10 (where CV% in CL was set to 0%). CVs for liver and brain volume and kidney weight were set to zero. Dy=dynamic (option in the Simcyp simulator)

Compatibility of Assigned WSV in Physiological Parameters with Observed WSV of PK: A Potential Solution?





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IDENTIFIABILITY ISSUE:

- **DISMISS IMPROBABLE SETS ✓** of WSV of Physiological Parameters of GI tract based on incompatibility with observed WSV of PK Parameters,

- **NO UNIQUE SET of WSV ×** for GI tract if only a single drug/formulation is used,

- **OBTAIN COMMPN SET (?)** by applying the process to several drugs & varying formulations which are sensitive to different elements of GI tract WSV

- **CCHECK AGAINST MEASURED WSV (?)** of GI tract physiology when these are available.

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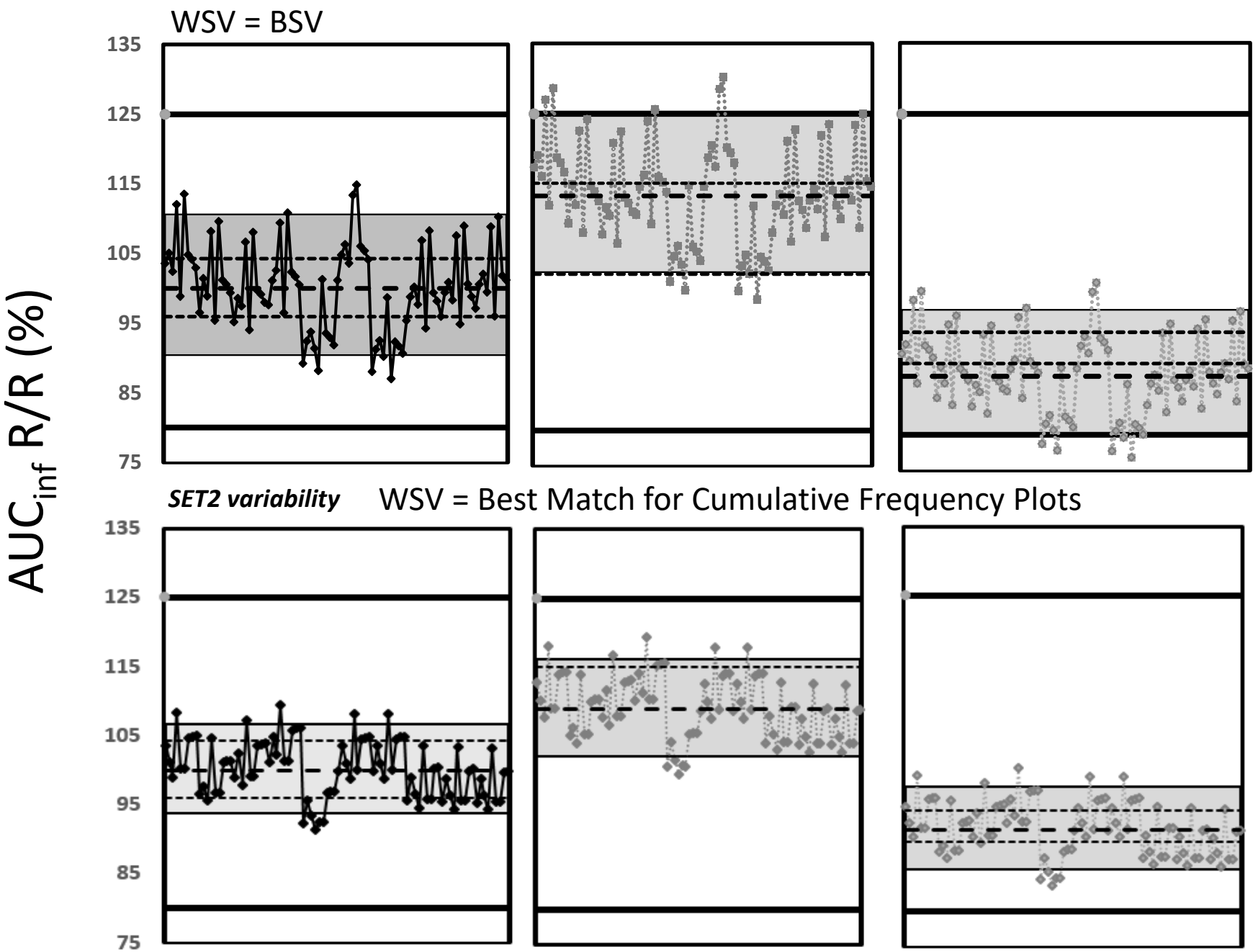
Observed vs Predicted Distributions (AUC, C_{max} and T_{max}) (Kolmogorov-Smirnov Test)

SET	D statistic AUC	Similarity (Y/N)	D statistic Cmax	Similarity Y/N)	D statistic Tmax	Similarity (Y/N)
(default)	0.350	No	0.417	No	0.200	Yes
1	0.200	Yes	0.217	Yes	0.150	Yes
2	0.167	Yes	0.150	Yes	0.217	Yes
3	0.367	No	0.367	No	0.217	Yes
4	0.133	Yes	0.200	Yes	0.133	Yes
5	0.267	No	0.317	No	0.183	Yes
6	0.183	Yes	0.250	No	0.167	Yes
7	0.217	Yes	0.167	Yes	0.133	Yes
8	0.167	Yes	0.167	Yes	0.183	Yes
9	0.233	Yes	0.317	No	0.200	Yes
10	0.217	Yes	0.233	Yes	0.183	Yes
11	0.200	Yes	0.183	Yes	0.133	Yes
12	0.300	No	0.250	No	0.133	Yes
13	0.317	No	0.333	No	0.217	Yes
14	0.133	Yes	0.167	Yes	0.217	Yes

Table - Comparison of simulated *vs* observed intra-subject variability (Full set of individuals, Kolmogorov-Smirnov test)



Multiple VBE Trials (with N Subjects in Each) to get the:

Likelihood of Passing the Criteria

- Likelihood
- BE Interval (80-125%)
- Predicted Outcomes
- Median of VBE's
- Overlay of Clinical Data

What Is the Right N for VBE?

(1?, …,6?, 12?, 24?, …, 1000?)

Applications: Model Drug/Formulation for Local VBE: Budesonide

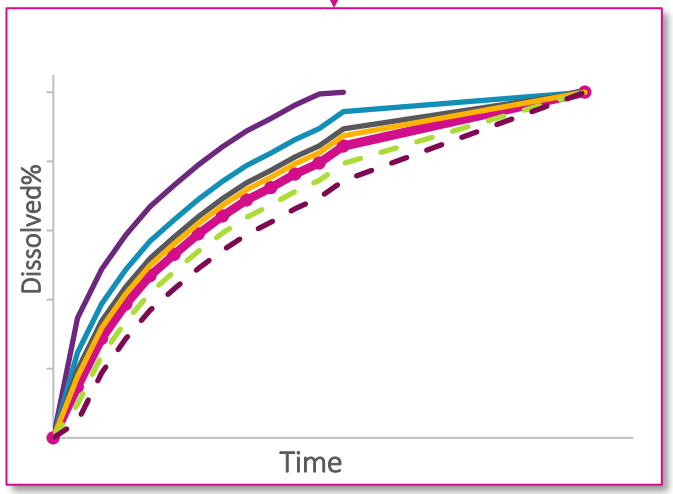
Dissolution

Intestinal microbiota metabolism

Absorption

First-pass metabolism

Plasma concentration



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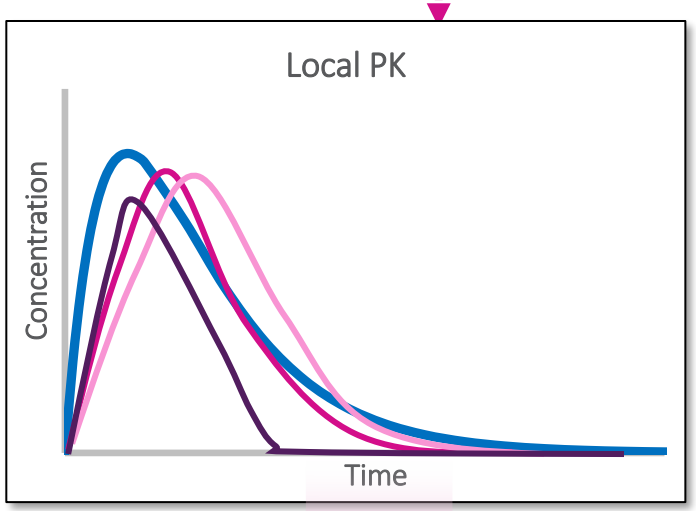

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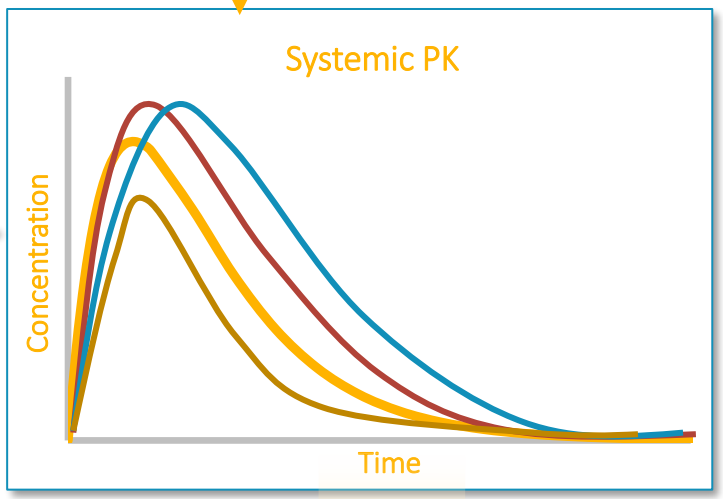
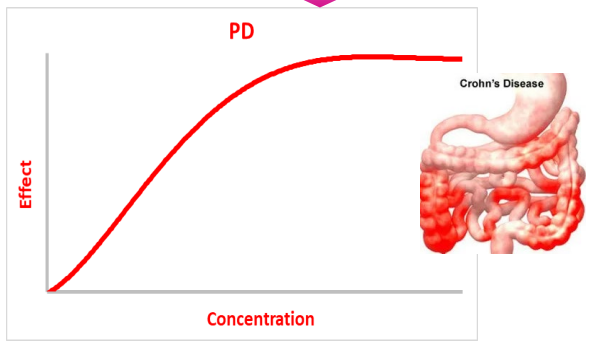


Similarity factor

$$f_2 = 50 \times log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}}}\right)$$



Safety

https://threadreaderapp.com/thread/1017945624023584770.html

pharmaceutics

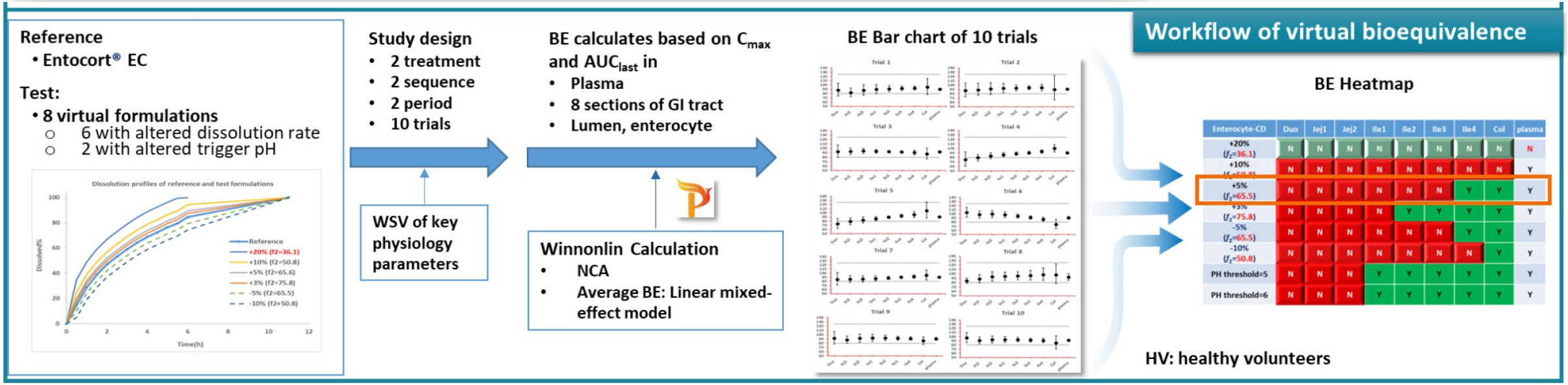
MDPI

Article

Harnessing the Power of Physiologically Based Pharmacokinetic Modeling to Explore Potential Discordance between in vitro Dissolution, Local Gut *vs* Systemic Bioequivalence in Health and Disease: The Case of Budesonide in Crohn's Disease

Chunyan Han [1,2,*], Tiancheng Sun [2], Sirikalyan Chirumamilla[3], Frederic Bois[3], Mandy Xu[2], Amin Rostami-Hodjegan[1,3,*]

Addressing Local Gut *vs* Systemic BE for Complex Generics in Health and Disease



BE Criteria: Heat Map for False/True Positive/Negative BE

- **Geometric mean of AUC and C_{max}**
- **VBE with 1 trial, 90% confidence intervals of T/R that fall within the limit of 80% - 125% indicate BE - VBE with 10 trials, if ≥ 8 out of 10 trials show bioequivalence, the formulation will be defined as BE.**

	Plasma	Local
True positive	BE	BE
True negative	NBE	NBE
False negative	NBE	BE
False positive	BE	NBE

VBE Results of Different Intestinal Segments vs Plasma in Healthy Volunteers

Enterocyte - HV		Duo	Jej1	Jej2	Ile1	Ile2	Ile3	Ile4	Col	plasma
+20% (f_2=36.1)	$AUC_{0\text{-last}}$	0%	0%	0%	0%	0%	0%	20%	0%	Y
	C_{max}	0%	0%	0%	0%	0%	0%	0%	40%	N
+10% (f_2=50.8)	$AUC_{0\text{-last}}$	0%	0%	0%	20%	20%	50%	70%	50%	Y
	C_{max}	0%	0%	0%	0%	20%	30%	60%	80%	N
+5% (f_2=65.5)	$AUC_{0\text{-last}}$	30%	40%	30%	60%	70%	80%	90%	70%	Y
	C_{max}	10%	50%	60%	60%	90%	90%	80%	100%	Y
+3% (f_2=75.8)	$AUC_{0\text{-last}}$	30%	70%	60%	70%	80%	90%	90%	80%	Y
	C_{max}	20%	80%	90%	90%	90%	90%	90%	100%	Y
-5% (f_2=65.5)	$AUC_{0\text{-last}}$	30%	40%	60%	70%	100%	90%	90%	100%	Y
	C_{max}	20%	30%	80%	80%	100%	90%	90%	100%	Y
-10% (f_2=50.8)	$AUC_{0\text{-last}}$	0%	0%	10%	20%	40%	60%	70%	70%	Y
	C_{max}	0%	0%	0%	0%	20%	30%	60%	100%	N
PH threshold=5	$AUC_{0\text{-last}}$	0%	50%	60%	80%	100%	90%	90%	100%	Y
	C_{max}	0%	60%	90%	100%	100%	90%	90%	100%	Y
PH threshold=6	$AUC_{0\text{-last}}$	10%	10%	20%	70%	100%	90%	90%	100%	Y
	C_{max}	10%	10%	30%	90%	90%	90%	80%	100%	Y

Combine AUC and C_{max} together

Enterocyte HV	Duodenum	Jejunum	Ileum	Colon	Plasma
20% (f_2=36.1)	N	N	N	N	N
10% (f_2=50.8)	N	N	N	N	N
5% (f_2=65.5)	N	N	N	N	Y
3% (f_2=75.8)	N	N	Y	Y	Y
-5% (f_2=65.5)	N	N	Y	Y	Y
-10% (f_2=50.8)	N	N	N	N	N
PH threshold=5	N	N	Y	Y	Y
PH threshold=6	N	N	Y	Y	Y

Bioequivalent locally | Green: true positive | pink: false negative | Light green: true negative | Red: false positive

VBE Results in Different Intestinal Segments vs Plasma in CD Patients

Enterocyte-CD		Duo	Jej1	Jej2	Ile1	Ile2	Ile3	Ile4	Col	plasma
+20% (f_2=36.1)	$AUC_{0\text{-last}}$	0%	0%	0%	0%	0%	0%	30%	0%	Y
	C_{max}	0%	0%	0%	0%	0%	0%	10%	70%	N
+10% (f_2=50.8)	$AUC_{0\text{-last}}$	0%	0%	0%	10%	20%	60%	70%	70%	Y
	C_{max}	0%	0%	0%	0%	30%	70%	90%	90%	Y
+5% (f_2=65.5)	$AUC_{0\text{-last}}$	50%	20%	20%	30%	70%	70%	90%	90%	Y
	C_{max}	10%	30%	40%	80%	80%	90%	90%	100%	Y
+3% (f_2=75.8)	$AUC_{0\text{-last}}$	60%	50%	30%	70%	80%	90%	90%	90%	Y
	C_{max}	40%	60%	80%	90%	90%	90%	90%	100%	Y
-5% (f_2=65.5)	$AUC_{0\text{-last}}$	50%	40%	40%	50%	60%	70%	90%	100%	Y
	C_{max}	40%	20%	40%	80%	80%	80%	90%	100%	Y
-10% (f_2=50.8)	$AUC_{0\text{-last}}$	0%	0%	0%	10%	30%	30%	50%	80%	Y
	C_{max}	0%	0%	0%	0%	0%	20%	50%	100%	Y
PH threshold=5	$AUC_{0\text{-last}}$	40%	30%	40%	80%	80%	90%	90%	100%	Y
	C_{max}	30%	70%	90%	90%	90%	90%	90%	100%	Y
PH threshold=6	$AUC_{0\text{-last}}$	10%	10%	20%	80%	80%	90%	90%	100%	Y
	C_{max}	0%	30%	60%	90%	90%	90%	90%	100%	Y

Combining AUC and C_{max} together

Enterocyte HV	Duodenum	Jejunum	Ileum	Colon	Plasma
20% (f_2=36.1)	N	N	N	N	N
10% (f_2=50.8)	N	N	N	N	Y
5% (f_2=65.5)	N	N	N	Y	Y
3% (f_2=75.8)	N	N	Y	Y	Y
-5% (f_2=65.5)	N	N	N	Y	Y
-10% (f_2=50.8)	N	N	N	Y	Y
PH threshold=5	N	N	Y	Y	Y
PH threshold=6	N	N	Y	Y	Y

Bioequivalent locally | Green: true positive | pink: false negative | Light green: true negative | Red: false positive

Conclusion – Incorporation of WSV in BE

(1) WSV in physiology propagates to PK and manifest itself as WSV in PK

(2) The same WSV of GI tract physiology cand lead to a varying WSV in PK for different formulations

(3) Hence; WSV of PK is NOT independent of Formulation

(4) Not all WSV for physiology of GI tract are measured (can be estimated)

(5) WSV of PK can be predicted using WSV of physiology via Population-Based PBPK platforms

(6) BE based on Systemic Circulation ≠ BE Based on the Local GutC-t profile

VBE - Systems Information & Workflow: Simcyp™ Biopharm:

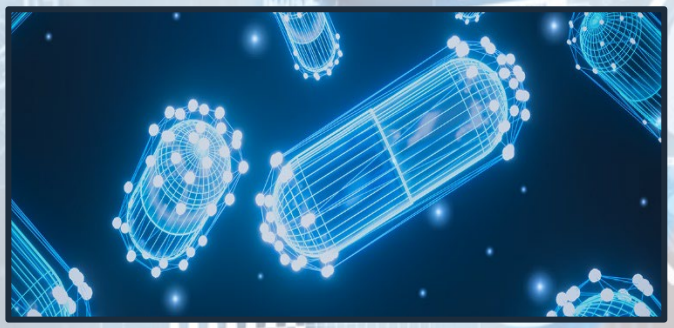
We've done the hard work, so you don't have to!

Features and Capabilities

GI Biology & Physiology

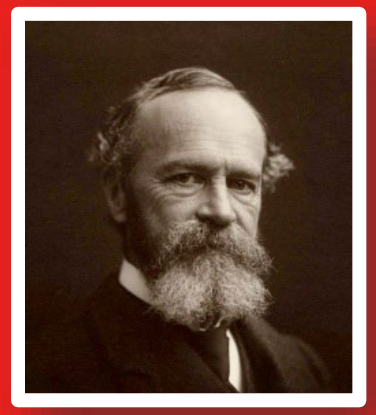
Automated VBE Workflow

Complex/Modified Formulations



Mechanistic IVIVC/IVIVE

Simcyp™ In Vitro Analysis (SIVA)



William James

When a thing was new, people said that it was not true;

When its truth could not be denied, people said it was not important;

When its importance could not be denied, people said that it was not new!

Thanks for Listening - Q&A over the Breakout