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Approaches in Establishing BE Safe Space for Oral Solid Dosage Form

FDA-CRCG 2022 workshop: Best Practices for Utilizing Modeling Approaches to Support Generic Product Development

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Disclaimer

The views expressed in this presentation are my own and do not represent the view of my employer.

Outline

- Definition of BE Safe Space and Application
- Different Methods to Establish BE Safe Space
  - Basic PBBM Workflow
  - Different Approach to Integrate In-vitro Data
- Case Study # 1: BE Safe Space to Supersede F2
- Case Study # 2: BE Safe Space to Wide Dissolution Specification- CRDS(Clinically Relevant Dissolution Specification)
- Summary

What is BE Safe Space and Application of Safe Space

- ✓ *A safe space is defined by the boundaries demarcated by in vitro specifications (i.e., dissolution or, other relevant drug product quality attributes), within which drug product variants are anticipated to be bioequivalent to one another and to the reference or target drug product (**here pivotal bio batch**)- US FDA guidance Oct 2020 (Draft): Use of PBPK-Biopharmaceutics Application….Manufacturing Changes and Control.*
  - ✓ Safe space can be expanded (Between Brand and Virtual) in presence of validated PBBM

BE Risk assessment & Selection of BE Batch for pivotal study- *Internal Decision making*

→

F2 Mismatch & Biowaiver for additional strength- *Regulatory Decision making*

↓

Set Clinically relevant drug product specification (Dissolution, PSD etc)- *Regulatory Decision making*

↓

Risk based biowaiver for post approval change- *Regulatory Decision making*

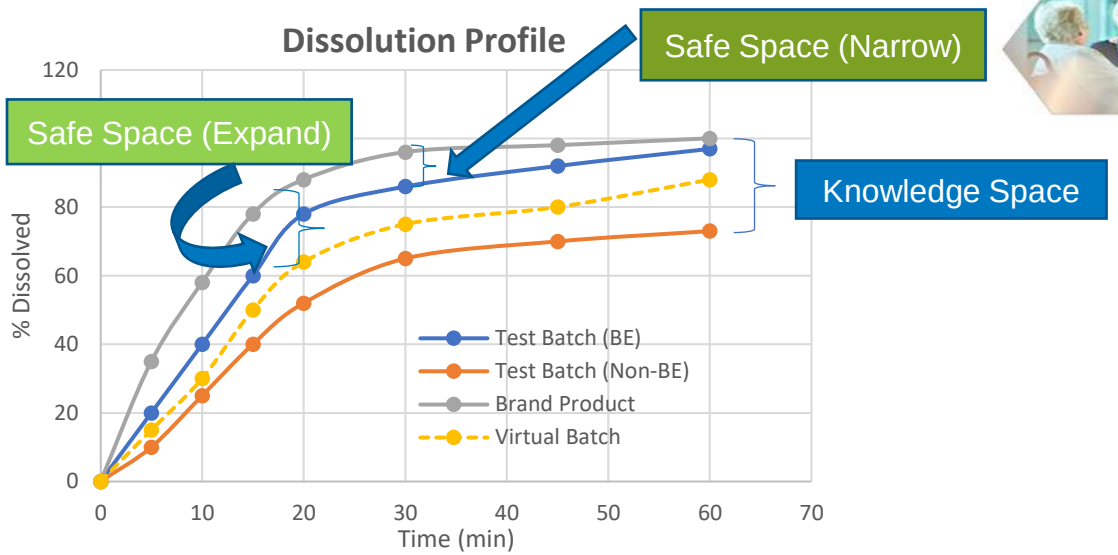
←

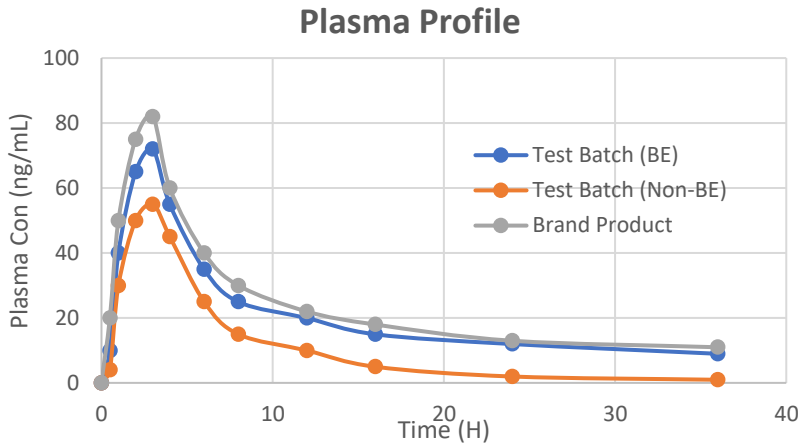
Food Effect Prediction (IR product)- Internal & *Regulatory Decision making*

↑

pH Mediated DDI (PPI)- **Internal** *Decision making Evaluation of gastric pH …DDI with Acid reducing agent… Nov 2020 (Draft)*

Application of BE Safe Space- Generic Industry





Different Methods to Establish BE Safe Space

BE Safe Space

(1) Pivotal BE Batch Data

BE studies linking CBA and in vivo responses are not available
Space is usually very narrow

(2) Bracketing Approach

BE study data with formulation variants are available
F2<50 but BE (between 2 test batch)
M&S Approach not required
Space is wider than (1)

(3) Conventional IVIVC

Numerical Deconvolution based Method (Level A):

- Batches with different release are available (At least 2).
- Linking in vitro & in-vivo by mathematical equation
- Useful for MR dosage form

Multiple level C

- At least 3 batches with different release required
- Lining PK Parameter with dissolution data at different time point by regression analysis (Y=mX+C)
- Useful for IR, where the level A is difficult due to different time scale between in-vitro & in-vivo

Extrapolate the data beyond Method 2 in presence of non-BE data (High Risk) or beyond KS (Low Risk)

(4) PBBM or Mechanistic IVIVR/C

- ✓ Integrating CBA dissolution, Physchem, Physiology
- ✓ Batches with different release (≥ 2) are required
- ✓ IVIVR can be used for any dosage form (IR + MR+DR)

Extrapolate the data beyond Method 2 in presence of non-BE data (High Risk) or beyond KS (Low Risk

Level of Confidence and Biopharmaceutics Understanding

M&S: Modelling & Simulation
KS- Knowledge Space
CBA- Critical Bioavailability Attribute

PBBM Workflow

Identify Objective (Question to be answered)

- Compound: Dose, logP, pKa, solubility, PSD
- Formulation: Dosage form, Precipitation, Dissolution Model
- Physiology: Fasting/Fed (ASF model)
- PK- UIR from IV/POP PK/oral solution

Model Development

- **Disposition Model-** IV or Oral Solution Data
- **Absorption Model:** Dose linearity study from literature
- **Incorporating in-vitro data** using ***In-house data with Pivotal BE Batch***
- Justify Dissolution model Approach (Direct approach, z-factor)
- % PE of individual Formulation ≤15%, Average ≤10%
- VBE (Pivotal BE Batch and Brand) to establish the similar BE Judgement (if possible)

Model Optimization/PSA
(e.g. PSD, Peff, Precipitation time, % fluid in GI, GI pH,, transit time, FuEnt, Z-factor, P-PSD, Weibull Parameter etc)

Model Validation

% PE of ≤ 10%
Rejection of non BE batch via VBE trial if possible

Generate Virtual Dissolution profile to identify edge of failure

Difference in predicted mean of PK Parameter (Between target and virtual) ≤ 20%
IVIVC Guidance FDA 1997

VBE trial (90% CI of PE between virtual profile and Target 0.80-1.25)
PBPK Guidance FDA 2020

Different Approach to Integrate In-vitro Data

Method	Pros/Eligibility	Cons/Limitation
Direct Input	➢ No Additional fitting ➢ Dissolution is independent of dissolution Condition (IR with BCS-I/III or ER osmotic system)	❖ Not Mechanistic and may not be suitable for IR with BCS-II/IV ❖ Not suitable for VBE trial
Weibull Model	➢ Fitting dissolution data into mathematical function (up to 3 phase) ➢ ER Tablet and IR product with BCS-I/III ➢ Useful for generating virtual dissolution profile (maintaining similar shape)	❖ Not Mechanistic can not be used for IR with BCS-II/IV ❖ Assume 1:1 correlation
Johnson Model	➢ Impact of API PSD can be assessed (Different kinetic solubility between different API polymorph/PSD) ➢ Mechanistic	❖ Formulation factor can not be assessed
Z-Factor	➢ Fitting Z factor (dissolution rate) to the dissolution data ➢ IR with BCS II/IV ➢ Constant z factor and pH vs Z factor ➢ Fitting initial point is a good approach- define the rate ➢ Useful for generating virtual dissolution profile	❖ Can not fit dissolution data with biphasic dissolution ❖ Can not fit Data with lag phase/plateau (coning) ❖ API PSD is ignored
P-PSD	➢ Extract PSD from formulation and use as input parameter using Johnson model ➢ Can fit biphasic dissolution (explain both rise and plateau)	❖ Complex calculation-need validation

Selection of Dissolution Model should be based on biopharmaceutics understanding and not based on best fitting

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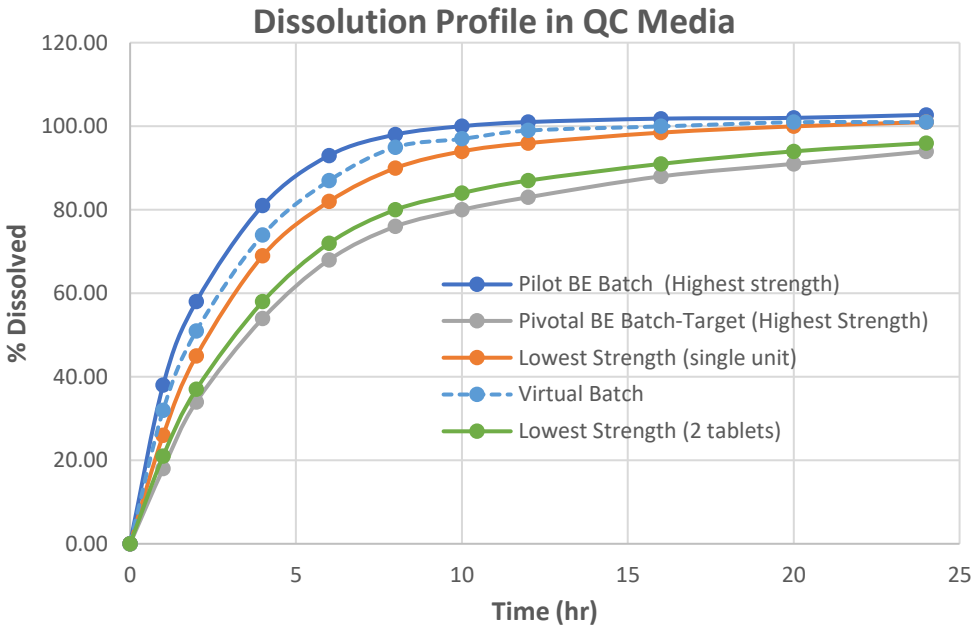
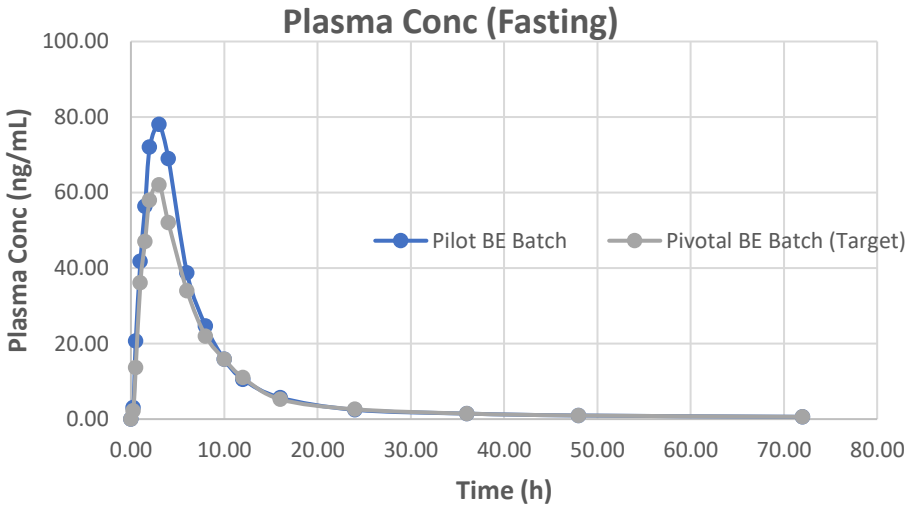
Case Study # 1: BE Safe Space to Supersede F2

Background Information

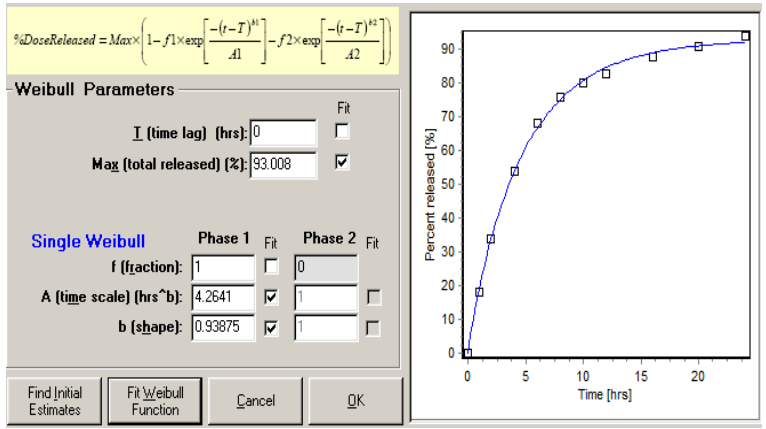
- ✓ **Formulation**: Extended Release Tablet
- ✓ **Available Strength**: Two Strengths
- ✓ BE study was performed on highest strength and biowaiver was applied for the lowest strength
- ✓ *Highest strength (Pivotal BE batch) vs lowest strength dissolution is NOT Similar (F2<50)- Strength dependent dissolution*
- ✓ **Objective** to develop a PBBM to justify F2<50 is not clinically relevant
  - ✓ Highly soluble and highly permeable drug substance (BCS-I)
  - ✓ PK is linear between two strength
- ✓ Available Batches for model development & Validation: Two (Pivotal BE Batch, non BE Batch- Pilot Batch)
  - ✓ Technology used in manufacturing both batches are same (Matrix) with different concentration of HPMC- Same release mechanism
- ✓ **Rank order relation**
- ✓ **Dissolution Profile between Target and Virtual Profile is the BE safe space- F2 is too stringent criteria**

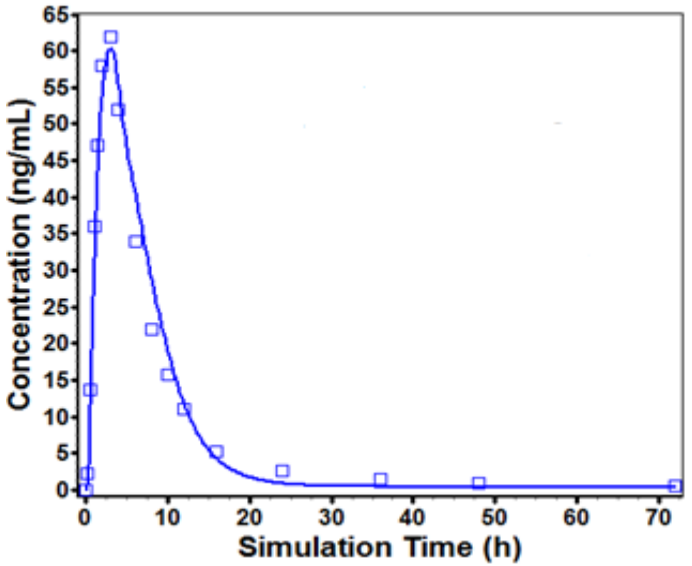




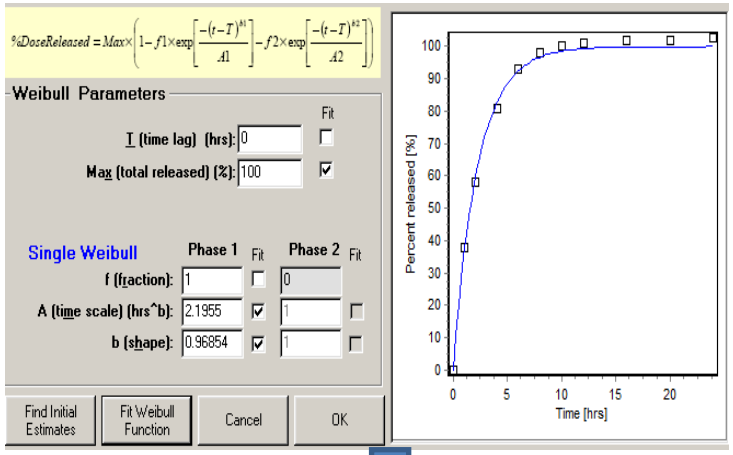
Model Development, Validation (Integrating Dissolution Data)

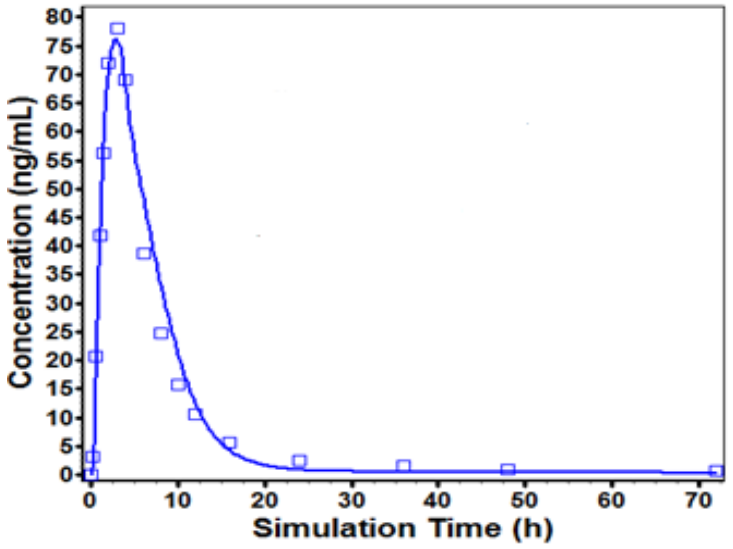
Pivotal BE Batch (Target)





Non BE Batch (Pilot)



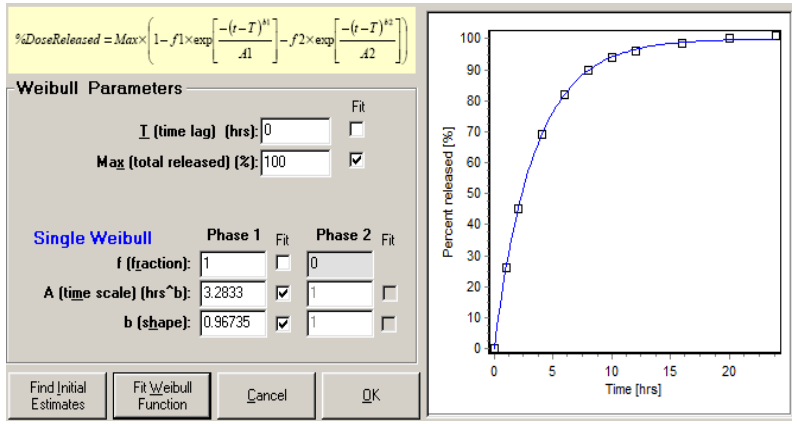


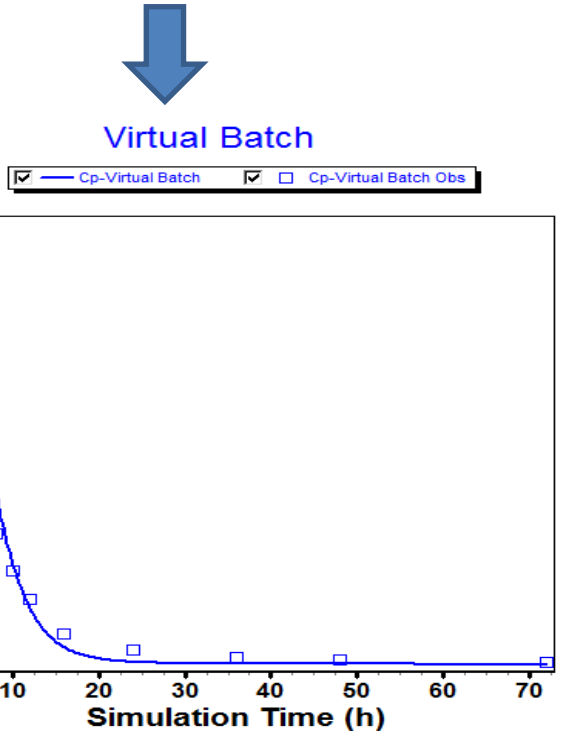
Parameter	Source
log P	ADMET
pKa	Literature
Solubility (mg/mL)	Measured
Caco-2 Papp (10-6 cm/s)	Literature
Peff (10-4 cm/s)	Converted from Papp
Particle size (µ)	Gastroplus Default
Precipitation Time (s)	Gastroplus Default
Physiology	*Default Fasting with an exception of Intestinal transit time*
CL (L/h/kg)	Fitting an oral solution
Vc (L/kg)	
K12 (1/h)	
k21 (1/h)	
B2P	Literature
Fup	Literature
Dissolution Model Weibull Model (Single Parameter) Dosage Form- CR Integral Tablet	

Model Development and Validation				
	PK	Observed	Predicted	% PE
Pivotal BE Batch (Target)	Cmax	60.3	62	2.82
	AUCt	509	478	6.09
Non-BE Batch (Pilot)	Cmax	78	76	2.56
	AUCt	586	569	2.90
Average	Cmax	2.5		
	AUCt	4.5		
Individual PE <15% and Average PE <10%				

Model Application (Integrating Dissolution Data)

Virtual Batch





- ✓ Dissolution profile of lowest strength (single unit) is the worst case
- ✓ Dissolution matches when lowest strength (2 units) compared against highest strength Pivotal batch
- ✓ PK is linear between lowest & highest strength
- ✓ Highest strength data can be extrapolated to lowest strength
- ✓ PBBM supersede F2 criteria

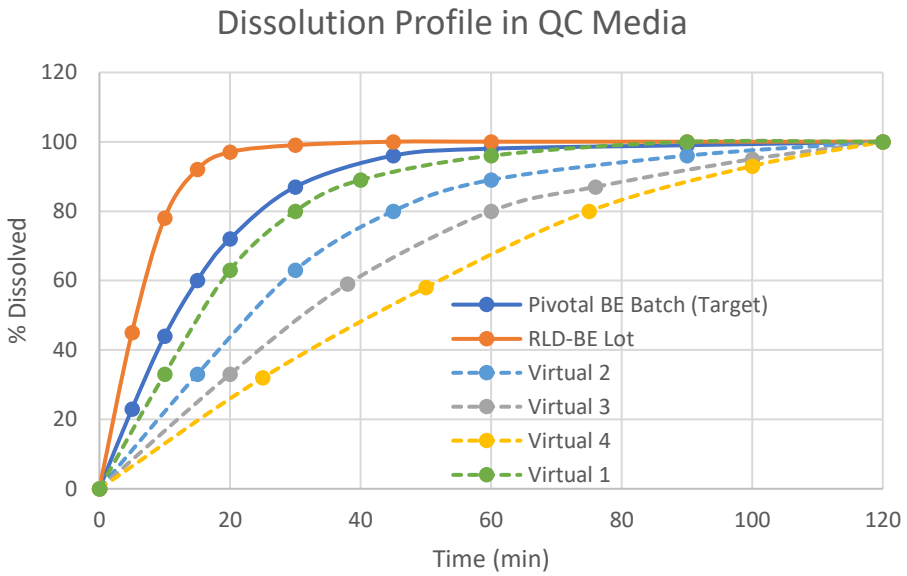
PK Parameter	Target Predicted Data (R)-Lower Bound	Virtual Batch Predicted Data (T)-Upper Bound	T/R (%)
C_{max}	60	71	118
AUC_t	478	489	103

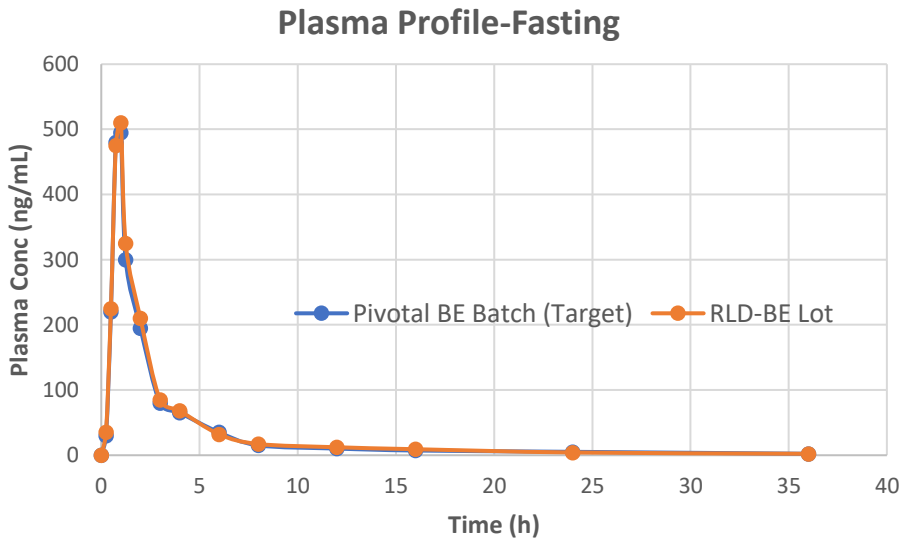
Conclusion: Dissolution profile between Lower and higher strength are anticipated to be Bioequivalent (falls within safe space)

Case Study # 2: BE Safe Space to Wide Dissolution Specification- CRDS (Clinically Relevant Dissolution Specification)

Background Information

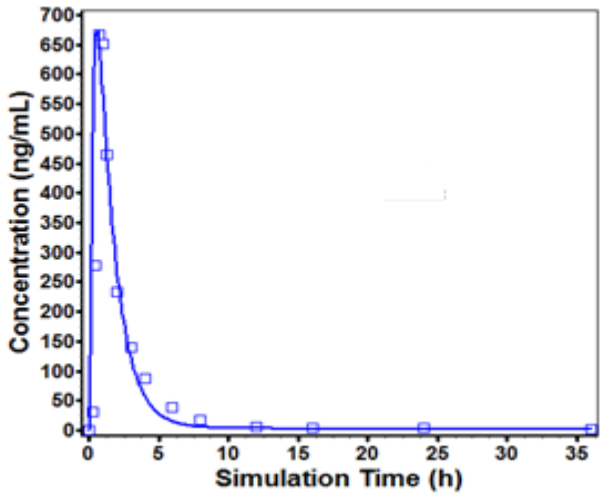
- ✓ **Formulation**: IR Capsule
- ✓ **Available Strength**: 2 strengths
- ✓ BE study was performed on highest strength
- ✓ *Dissolution SPEC was set at Q=80% in 45 minutes (Agency recommend to tight it to Q=80% in 30 minutes)*
- ✓ **Objective** to develop a PBBM to set the clinically relevant dissolution specification (Q=80% in 45 minutes)
- ✓ Highly soluble and moderate permeable drug substance (BCS-III)
- ✓ Available Batches for model development & Validation: Literature (Oral solution, 3 IR capsule at different dose) and Pivotal BE Study data (Pivotal BE Batch and RLD)
  - ✓ Dissolution is not rate limiting
  - ✓ BE with 2 test formulation with rank order was not available
- ✓ **Virtual profiles were created by using different scale factor to Pivotal BE batch data (Virtual 1, Virtual 2, Virtual 3, Virtual 4- 80% in 30 min, 45 min, 60 min and 75 minutes respectively**
- ✓ **Dissolution Profile between Target and Virtual Profile 2 is the BE safe space- CRDS (Q =80% in 45 minutes justified)**



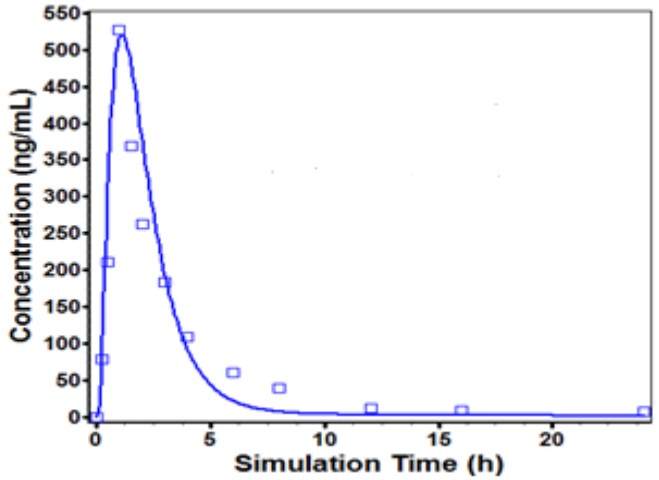


Model Development & Validation-Literature Data (No Dissolution Data)

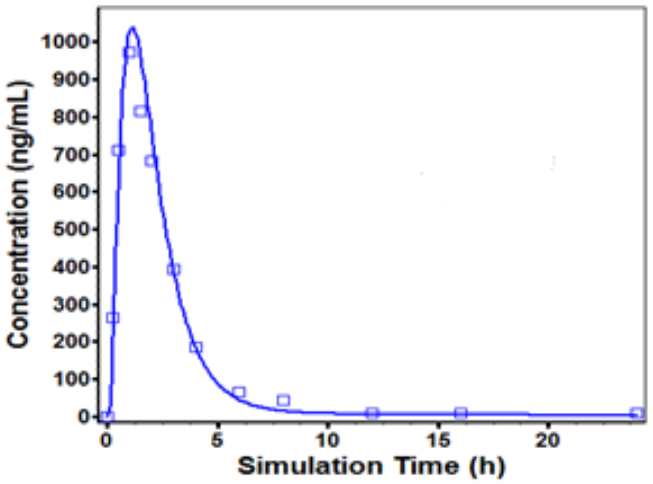
Oral Solution (Dose same as BE Batch)



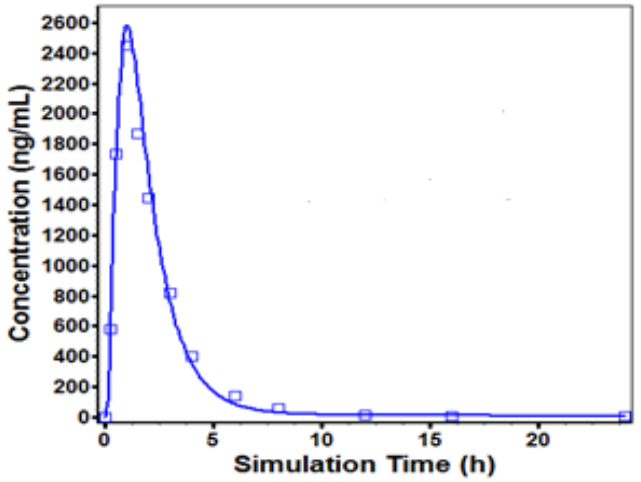
IR Capsule (Dose 1)



IR Capsule (Dose 2)



IR Capsule (Dose 3)

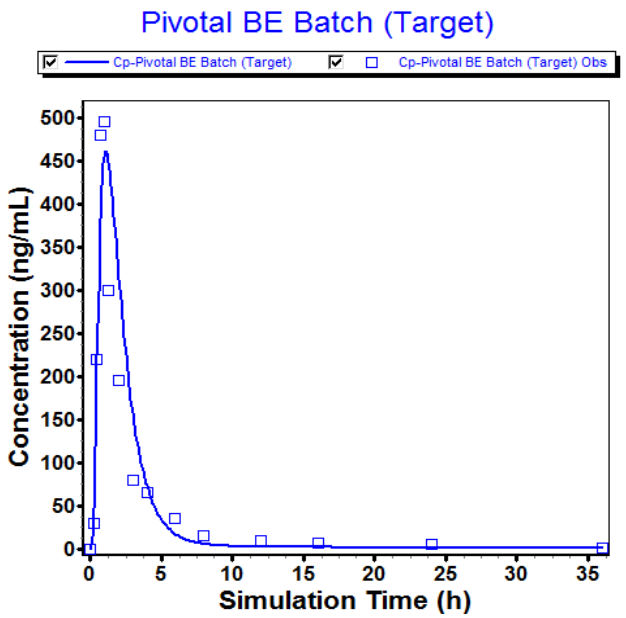


Parameter	Source
log P	ADMET
pKa	Literature
Solubility (mg/mL)	Measured
Peff (10-4 cm/s)	Fitting Oral Solution
Particle size (µ)	Gastroplus Default
Precipitation Time (s)	Gastroplus Default
Physiology	Default Fasting
CL (L/h/kg)	Fitting an IV Infusion
Vc (L/kg)	
K12 (1/h)	
k21 (1/h)	
B2P	Literature
Fup	Literature
Dissolution Model: Johnson; Dosage form- IR Capsule	

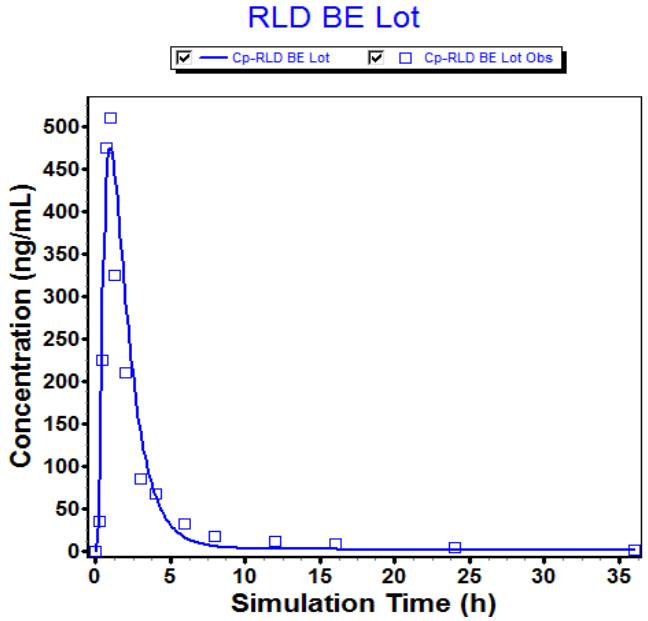
Baseline Model Development & Validation-Literature				
	PK	**Observed**	**Predicted**	**% PE**
Oral Solution	Cmax	666	674	1.20
	AUCt	1338	1324	1.05
IR Capsule Literature (Dose 1)	Cmax	526	520	1.14
	AUCt	1462	1341	8.28
IR Capsule Literature (Dose 2)	Cmax	973	1039	6.78
	AUCt	2807	2682	4.45
IR Capsule Literature (Dose 3)	Cmax	2447	2581	5.48
	AUCt	6081	6037	0.72
Average	Cmax	3.65		
	AUCt	3.62		
Individual PE <15% and Average PE <10%				

Model Development & Validation-In-house Data (Integrating Dissolution Data)

Pivotal BE Batch (Target)



RLD BE lot

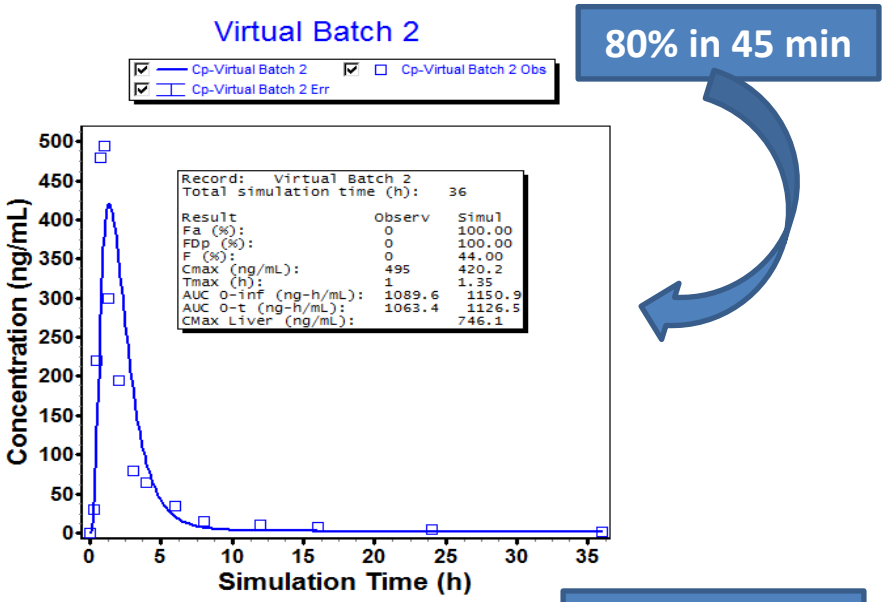


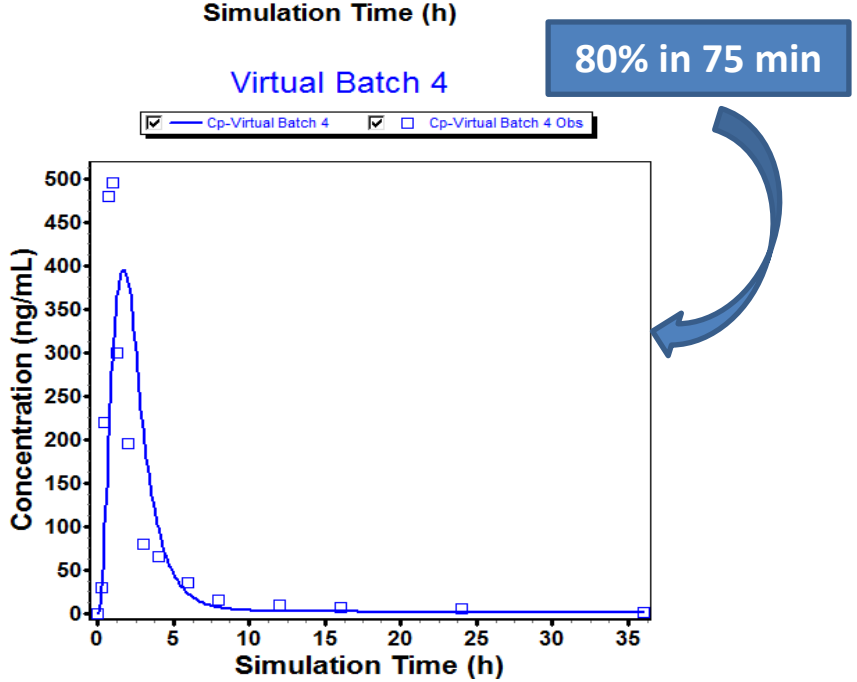
Parameter	Source
log P	ADMET
pKa	Literature
Solubility (mg/mL)	Measured
Peff (10-4 cm/s)	Fitting Oral Solution
Particle size (μ)	Gastroplus Default
Precipitation Time (s)	Gastroplus Default
Physiology	Default Fasting
CL (L/h/kg)	Fitting an IV Infusion
Vc (L/kg)	
K12 (1/h)	
k21 (1/h)	
B2P	Literature
Fup	Literature
Dissolution Model: Direct Input; Dosage form- CR Dispersed	

PK Parameter	Observed Data (Pivotal BE study, N=28)			Predicted T/R
	T/R	Lower CI	Upper CI	
Cmax	96	90	106	98
AUCt	103	97	107	100
Same BE judgement integrating the dissolution data- Bio-predictive				

Model Development and Validation with In-house BE data (Pivotal)-Integrating Dissolution Data				
	PK	**Observed**	**Predicted**	**% PE**
Pivotal BE Batch (Target)	Cmax	495	460	7
	AUCt	1063	1126	5.93
RLD (BE lot)	Cmax	510	475	6.86
	AUCt	1113	1126	1.17
Average	Cmax	7		
	AUCt	3.5		
Individual PE <15% and Average PE <10%				

Model Application (Integrating Dissolution Data)





- ✓ Integrating the dissolution data of the virtual Batches as direct input
- ✓ Dissolution profile between the Target & Virtual 2 was set as safe space
- ✓ Expanding safe space beyond the knowledge space is OK
  - ✓ Low Biopharmaceutics risk considering the BCS –III/IR product and dissolution is not rate limiting
- ✓ PK is linear and increase mode confidence using data from different dosage form and dose
- ✓ BE safe space can be utilised for the commercial batch manufacturing
- ✓ Q=80% in 45 minutes anticipated to be Bioequivalent was set as CRDS

PK	T/R (T- Virtual Batches, R- Pivotal BE Batch)			
	Virtual 1	**Virtual 2**	**Virtual 3**	**Virtual 4**
Cmax	98	91	85	84
AUCt	100	100	100	100
Spec	80% in 30 min	80% in 45 min	80% in 60 min	80% in 75 min

All virtual Batches are anticipated to be BE based on Min/Max (Cmax and AUC) <20%

Virtual 3 and 4 is towards edge of failure considering the upper and lower CI and ISCV from Pivotal study

Summary

- In vitro data can be integrated by mechanistic/non mechanistic way
- Best Practice to use the P_{eff} by fitting an oral solution plasma profile
- PSA for Physiological parameter are often useful to capture the accurate Tmax/absorption for MR products.
- BE safe space can be extended beyond knowledge safe space for low biopharmaceutics risk product (BCS-I/III IR)
- BE data of more than one test formulation (including non-BE batch) may not be available all the time.
- BE safe space useful for product lifecycle management.
- Min/max <20% or Virtual BE trial along with sensitivity analysis to establish the BE safe space

References

- Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations- US FDA Sep 1997
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Thank You