

How to Use Modeling and Simulation to Link In Vitro Dissolution to Drugs' In Vivo Behavior

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APS

Developing Clinically Relevant
Dissolution Specifications (CRDS) for Oral Drug Products
June 15th, 2021



The Academy of
Pharmaceutical Sciences



[illegible]

Simulations Plus – Technology Offerings

Discovery	Preclinical	Clinical
MedChem Designer™		• Eliminate PI • Support the • Eliminate pe
ADMET Predictor™		
GastroPlus™		
	DDDPlus™	
	MembranePlus™	
	PKPlus™	
	DILIsym™	
	IPFsym™	
	RENAsym™	
	NAFLDsym™	
	RADAsym™	
	Monolix Suite™	
Consulting Services		KIWI™

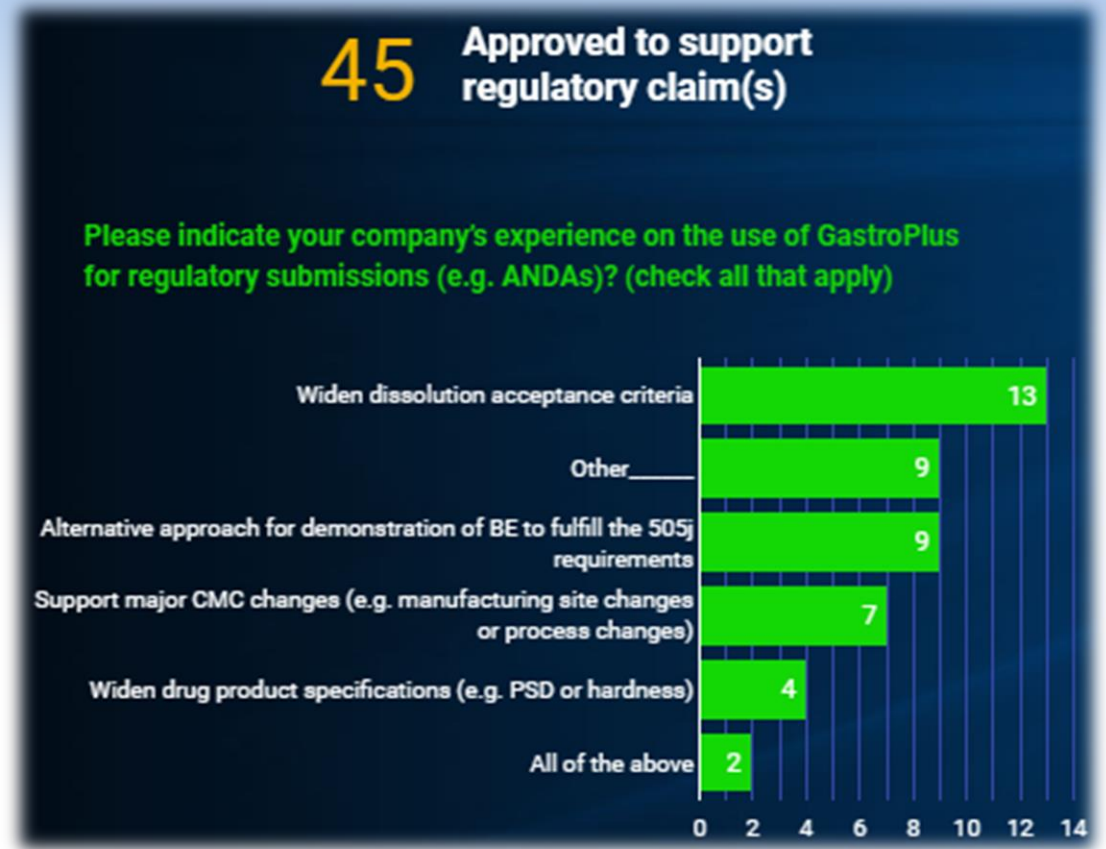
GastroPlus®



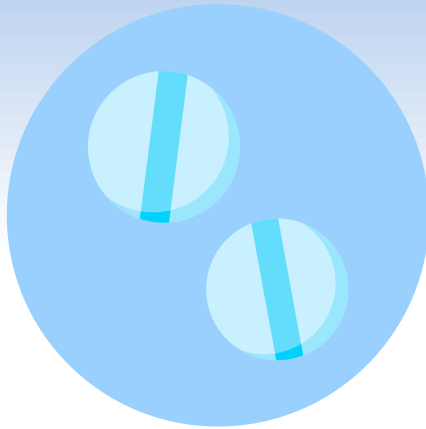
Mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal, subcutaneous, intraarticular and intramuscular absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals.

2020 generic drug company survey

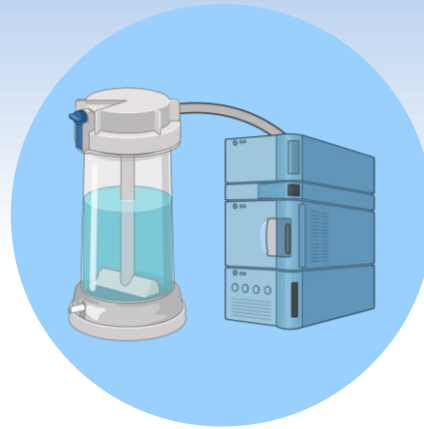
- Surveyed >30 generic drug companies licensing GastroPlus and/or working with our consulting teams
- Invited responses to:
 - Guide GastroPlus R&D activities heading into 2021
 - Describe use cases and regulatory interactions with GastroPlus to support ANDAs or 505j requirements



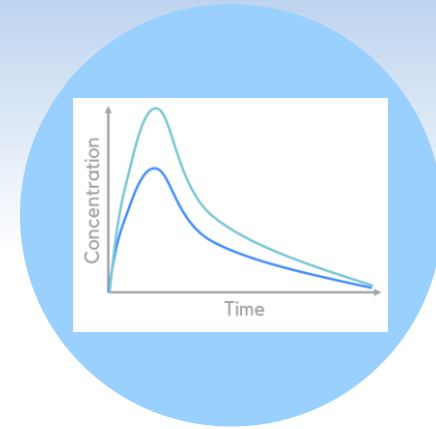
The goal: predict *In Vivo* PK



Formulation

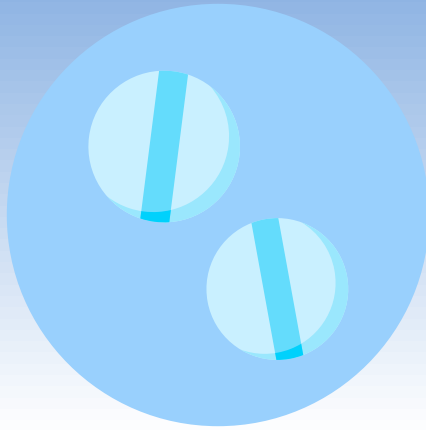


In Vitro

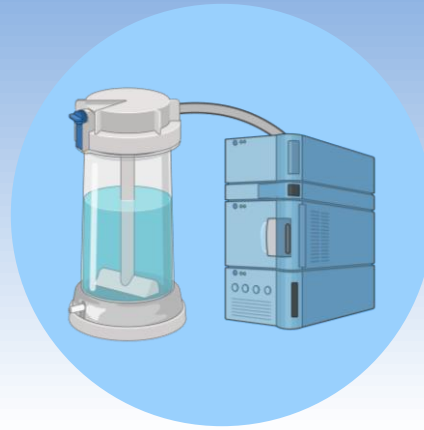


In Vivo

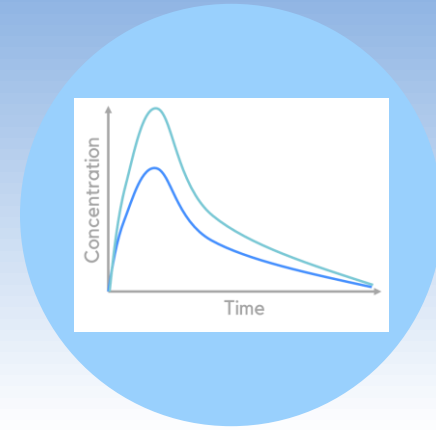
The goal: predict *In Vivo* PK



Formulation



In Vitro

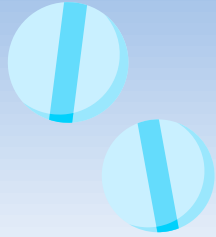


In Vivo

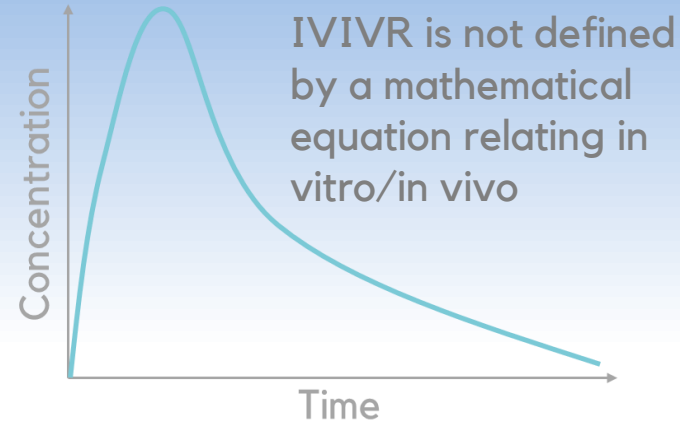


Predict *In Vivo* PK: framework

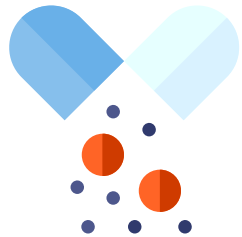
Immediate release



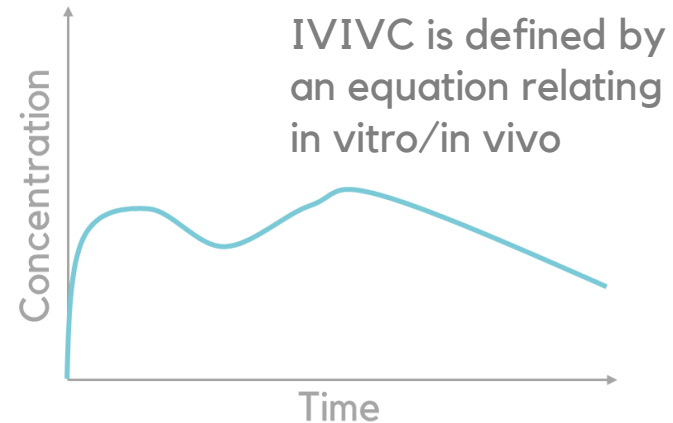
PBBM –IVIV Relationship



Modified release



PBBM –IVIV Correlation



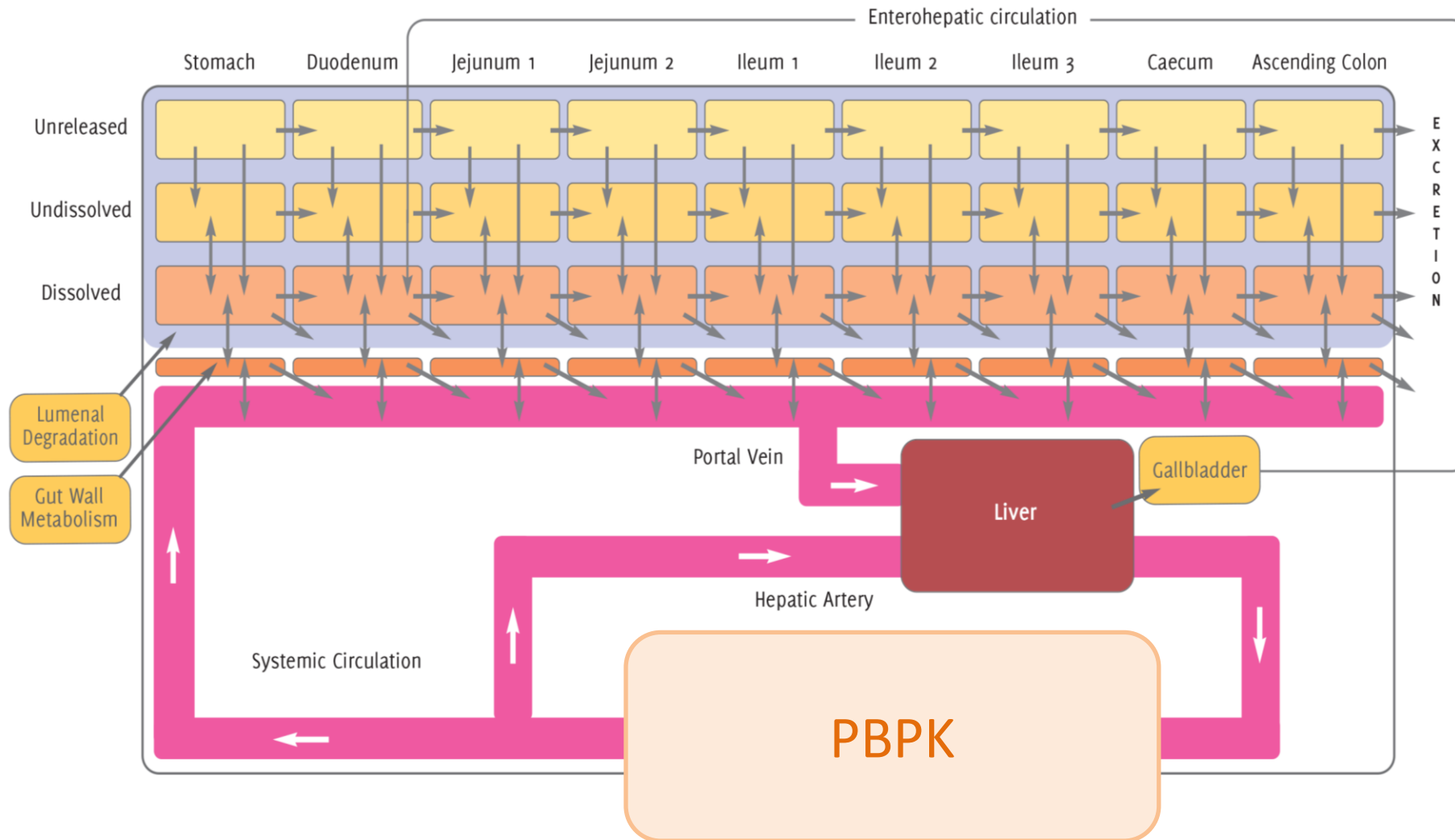
Virtual Bioequivalence



CRDS

PBBM & GastroPlus

Advanced Compartmental Absorption and Transit Model (ACAT™)



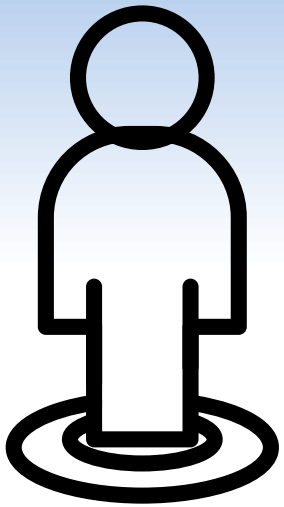
Virtual BE & GastroPlus



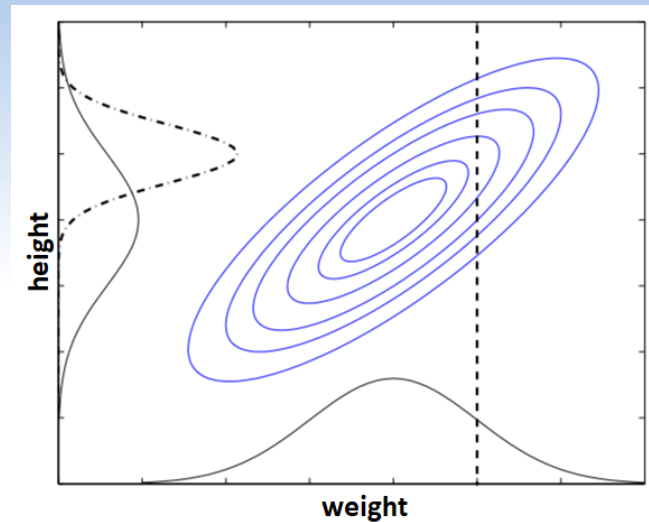
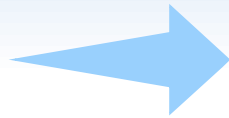
- Population of up to 2500 subjects
- Populations are generated, not sampled from a database
 - An infinite number of populations is possible
- Subjects are generated by Monte Carlo sampling of selected parameters within their defined distributions:
 - Gut physiology parameters
 - Pharmacokinetic parameters
 - PBPK parameters
 - Dosage form and compound parameters
- Populations can be saved and reused for crossover studies
- Possible to include intrasubject variability



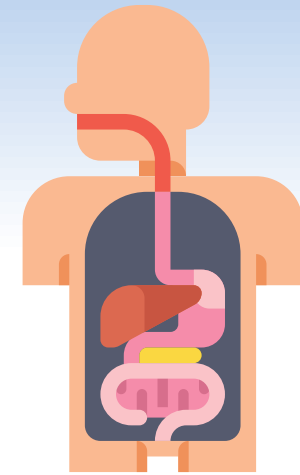
Virtual BE & GastroPlus



Randomly select age and gender from defined population



Select body weight and height for the subject based on bivariate distribution for given age and gender

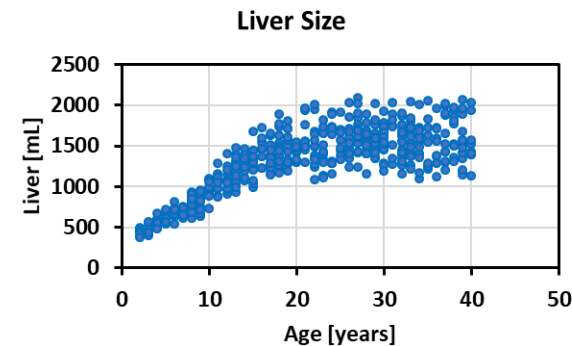
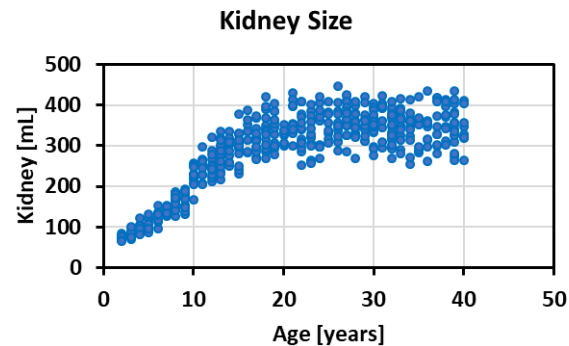
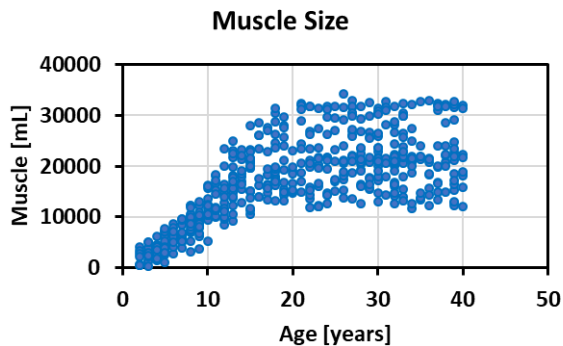
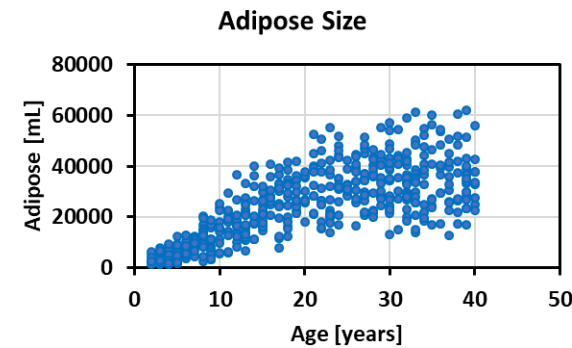
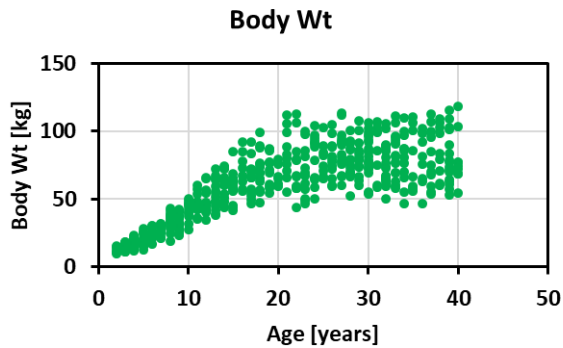


Generate the physiology with the tissue sizes corresponding to the selected age, gender, height and weight

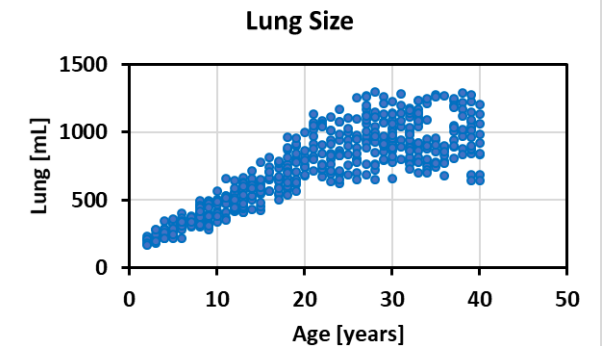


Virtual BE & GastroPlus

Population of 500 subjects; 2-40 years old; 50% males;
body weight from 60-140% of typical weight, BMI up to 32



- Can generate wider range of body weights (more realistic general population)
- Includes variability on body heights
- Have more options for creating populations of subjects

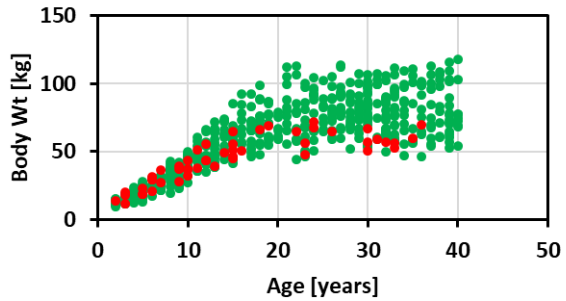




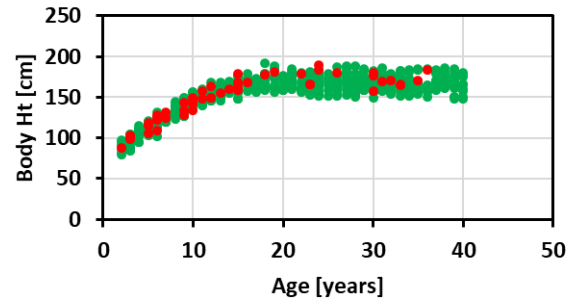
Virtual BE & GastroPlus

Population of 50 subjects; 2-40 years old; 50% males;
body weight from 60-140% of typical weight, BMI up to 21

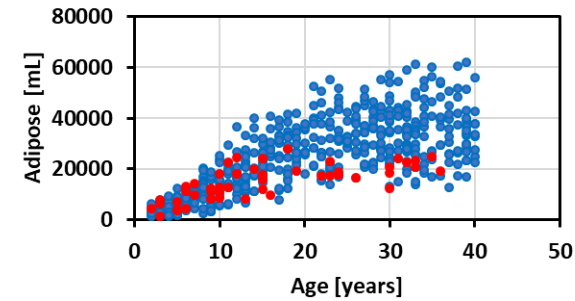
Body Wt



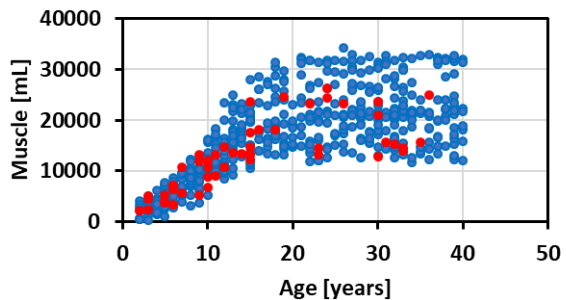
Body Ht



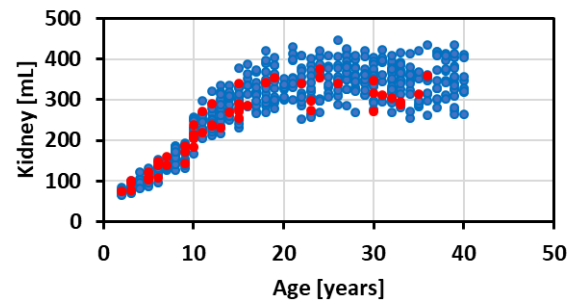
Adipose Size



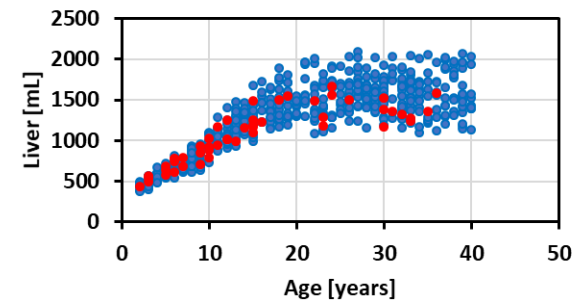
Muscle Size



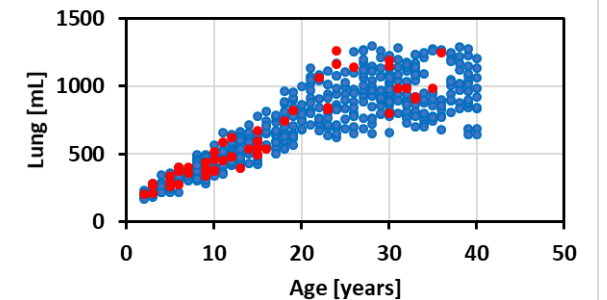
Kidney Size



Liver Size



Lung Size



Intra-subject variability

Population Simulator

File

Parameters

Clear All

Add All

Add Select

Set Defaults

Population

Set PEAR

Load Previous

Create New

Select Outputs

Previous Pop run:
Propranolol HCl
BE-12Subjects_Tri

GastroPlus(TM)
v.9.7.0038
Population
Simulator File
9/27/2020
11:17:17 AM

Drug Name/ID =
Propranolol HCl
BE

Parameter	Lower Limit	Mean Value	Upper Limit	CV%	Distribution
Subsequent Dose of Propranolol H	128.38	140.28	153.29	3	Log-Normal
Dose of Propranolol HCl BE (mg)	128.38	140.28	153.29	3	Log-Normal
Primary Permeability of Propranolol	0.6478	2.91	13.072	65	Log-Normal
Particle Shape Factor of form 1 Of F	0.7513	1	1.331	10	Log-Normal
Mean Drug Particle Radius of form	18.783	25	33.275	10	Log-Normal
Precipitation Particle Radius of Proj	18.783	25	33.275	10	Log-Normal
Precipitation Time of Propranolol H	676.18	900	1197.9	10	Log-Normal
Reference Solubility of Propranolol	93.914	125	166.38	10	Log-Normal
Fraction Unbound in Enterocytes o	0.7513	1	1	10	Log-Normal
Oral Transit Time of Propranolol HC	0.1878	0.25	0.3328	10	Log-Normal
Oral Cavity ASF Propranolol HCl BE	0.7513	1	1.331	10	Log-Normal
Duodenum ASF Propranolol HCl BE	2.0488	2.727	3.6296	10	Log-Normal
Jejunum 1 ASF Propranolol HCl BE	2.0123	2.6783	3.5649	10	Log-Normal
Jejunum 2 ASF Propranolol HCl BE	2.0099	2.6752	3.5607	10	Log-Normal
Ileum 1 ASF Propranolol HCl BE	1.9833	2.6398	3.5135	10	Log-Normal
Ileum 2 ASF Propranolol HCl BE	1.9693	2.6211	3.4887	10	Log-Normal
Ileum 3 ASF Propranolol HCl BE	1.9455	2.5894	3.4465	10	Log-Normal
Caecum ASF Propranolol HCl BE	0.2641	0.3515	0.4679	10	Log-Normal
Asc Colon ASF Propranolol HCl BE	0.6187	0.8234	1.096	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)	189.82	315.86	525.6	18.5	Log-Normal
Caecum Length (cm)	7.0815	13.502	25.743	24	Log-Normal
Colon Length (cm)	14.87	28.352	54.057	24	Log-Normal
Stomach Volume (mL)	25.659	48.923	93.277	24	Log-Normal
Small Intestine Radius (cm)	0.8494	1.2263	1.7703	13.02	Log-Normal
Caecum Radius (cm)	2.1073	3.4501	5.6485	17.86	Log-Normal
Colon Radius (cm)	1.2485	2.4519	4.8153	25.23	Log-Normal
Stomach Transit Time (h)	0.0559	0.25	1.119	64.8	Log-Normal
Small Intestine Transit Time (h)	1.2315	3.2279	8.4612	37.88	Log-Normal

Dose is defined in:

☒ mg ☐ mg/kg ☐ mg/m²

Output Points 300

Repeated Trials 10

Sample Size (Maximum = 2500) 12

☐ Use this run as reference in BE calculations

Intrasubject Settings

☒ No Intrasubject Variability

☐ Simulate Physiologic Intrasubject Variability

☐ Apply Intrasubject CV% to C_{max} and AUC

Sampling Distribution Normal Normal

CV % 10 10

OK Cancel

No intrasubject variability

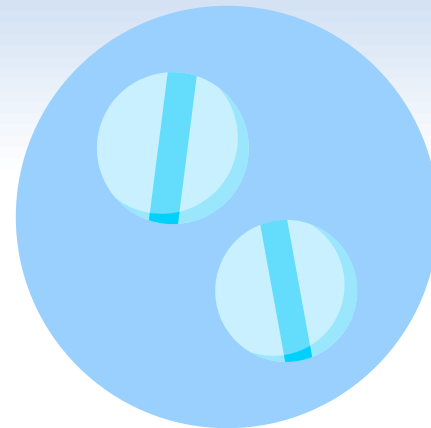
- same subject parameters as in previous versions of GastroPlus

Intrasubject variability on input parameters

- Transit time, intestinal volume, pH, and bile salt concentration

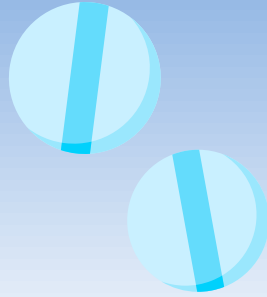
Intrasubject variability on the resulting C_{max} and AUCs

- Using Monte-Carlo sampling
- Can have different CVs for C_{max} and AUC



IR Formulation

IR: dissolution



Johnson Model

$$\frac{dM_D}{dt} = \frac{D_w}{\rho r_t T} \frac{(1 + 2s)}{s} (C_s - C_l) M_{u,t}$$

D_w = diffusion coefficient

C_s = solubility at local pH

C_l = lumen concentration

ρ = particle density (density of API crystals)

r_t = spherical particle radius for particle size bin j

T = diffusion layer thickness

s = shape factor

Z-factor Model

$$\frac{dM_D}{dt} = z M_{u,0} \left(\frac{M_{u,t}}{M_{u,0}} \right)^{2/3} (C_s - C_l)$$

z represents $\frac{3D_w}{\rho r T}$ and is determined by fitting to in

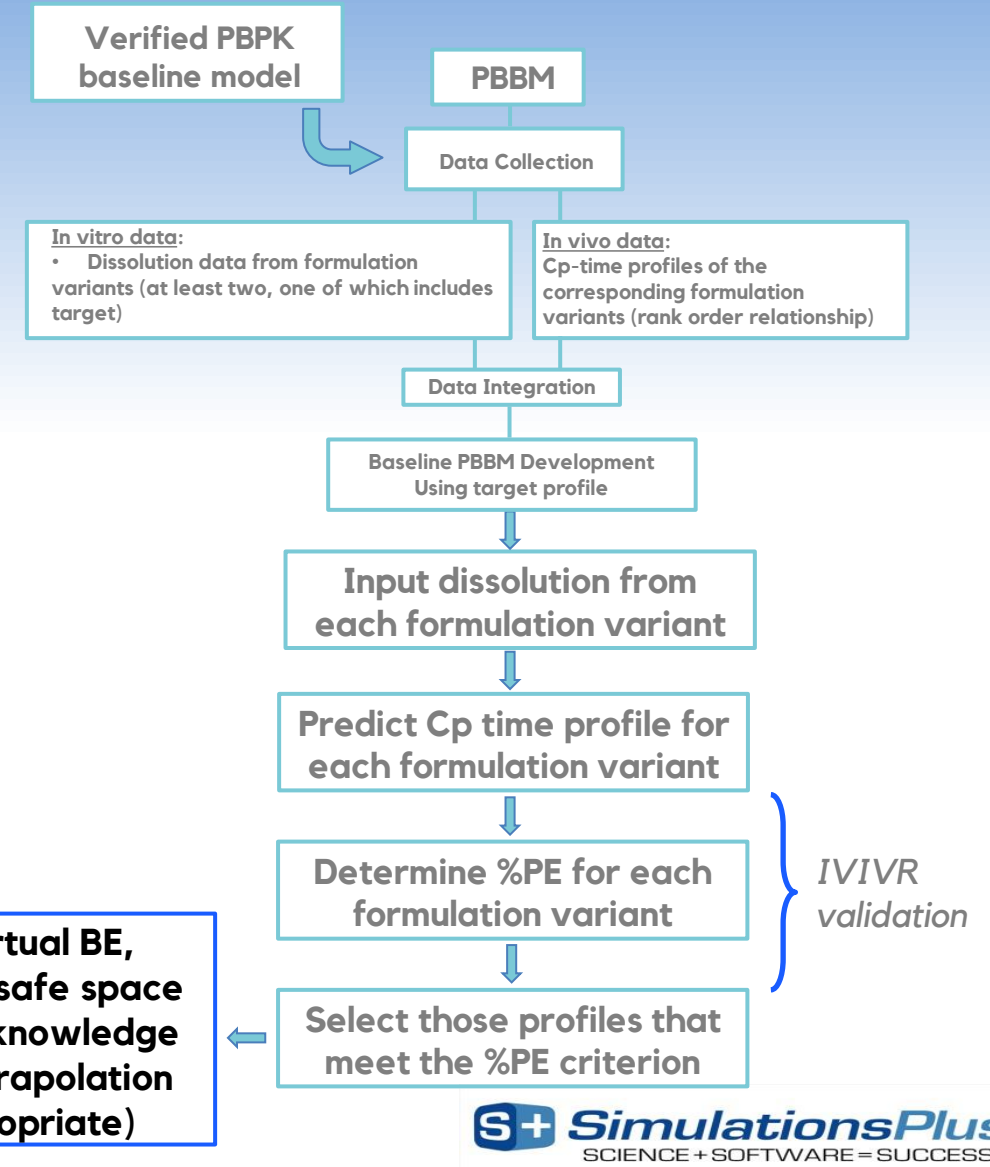
vitro dissolution data

In vitro experimental settings are required

IVIVR establishment

- Process for determining the link between CMAs/CPPs/CFVs and a response derived from an in vitro dissolution and its in vivo impact
- To have regulatory application, this response should be a surface response derived from evaluating several formulation variants around the target profile

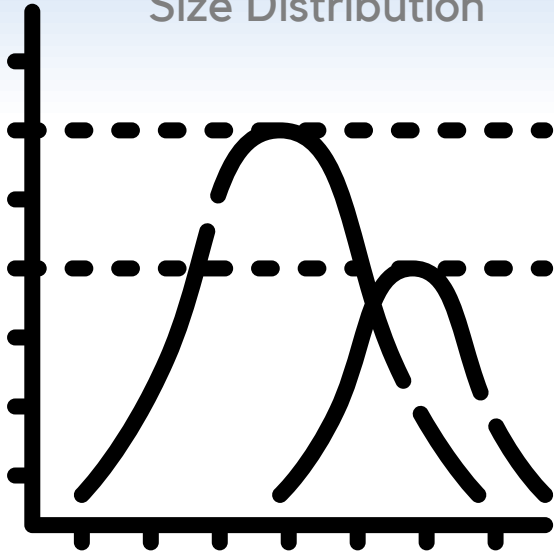
➔ Critical to determine the **predictive** ability of the dissolution method **within this range**



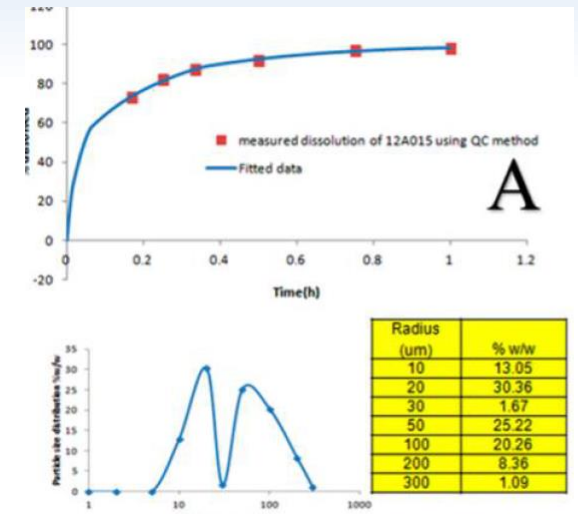
IR: dissolution

Johnson Model

In Vitro Particle Size Distribution



Fitted Particle Size Distribution



In Vivo PK Prediction

Pepin et al. 2016

Case Study

Crossover trials to show Bioequivalence
after manufacturing changes

Objectives

Context:

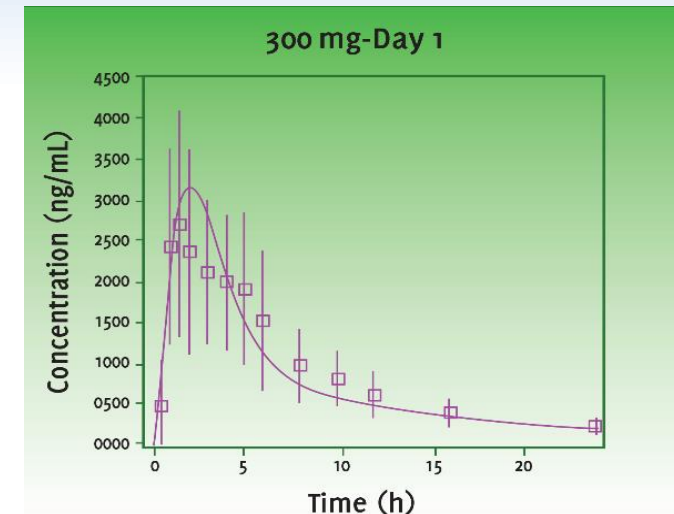
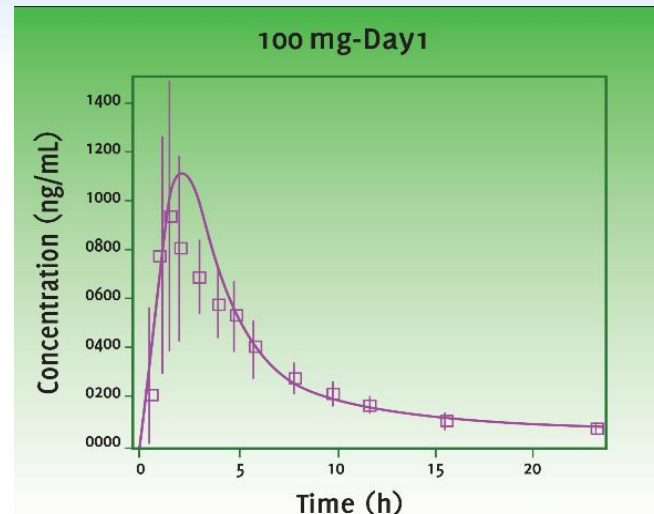
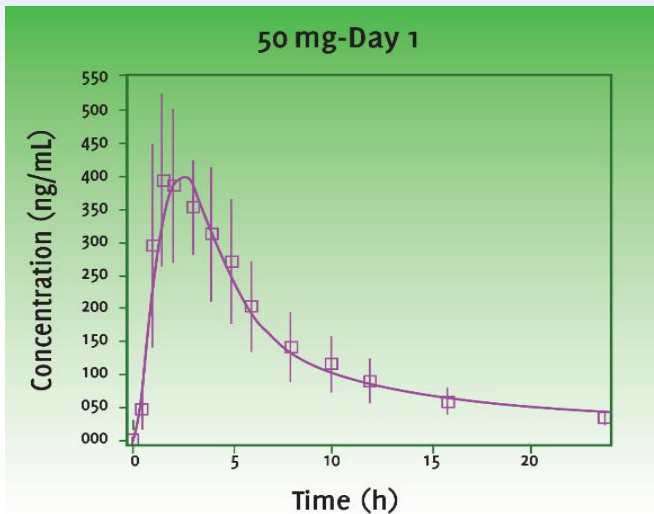
- Post-approval, sponsor's manufacturing process changes resulted in different particle size distributions for new lots: Inline milling step added to crystallization process (PE)

Modeling and Simulations (M&S) to request a biowaiver by:

- Assessing the effects of changes in particle size distribution of the active pharmaceutical ingredient (API) on its oral bioavailability
- Predicting the virtual bioequivalence between the "new" and "old" API lots

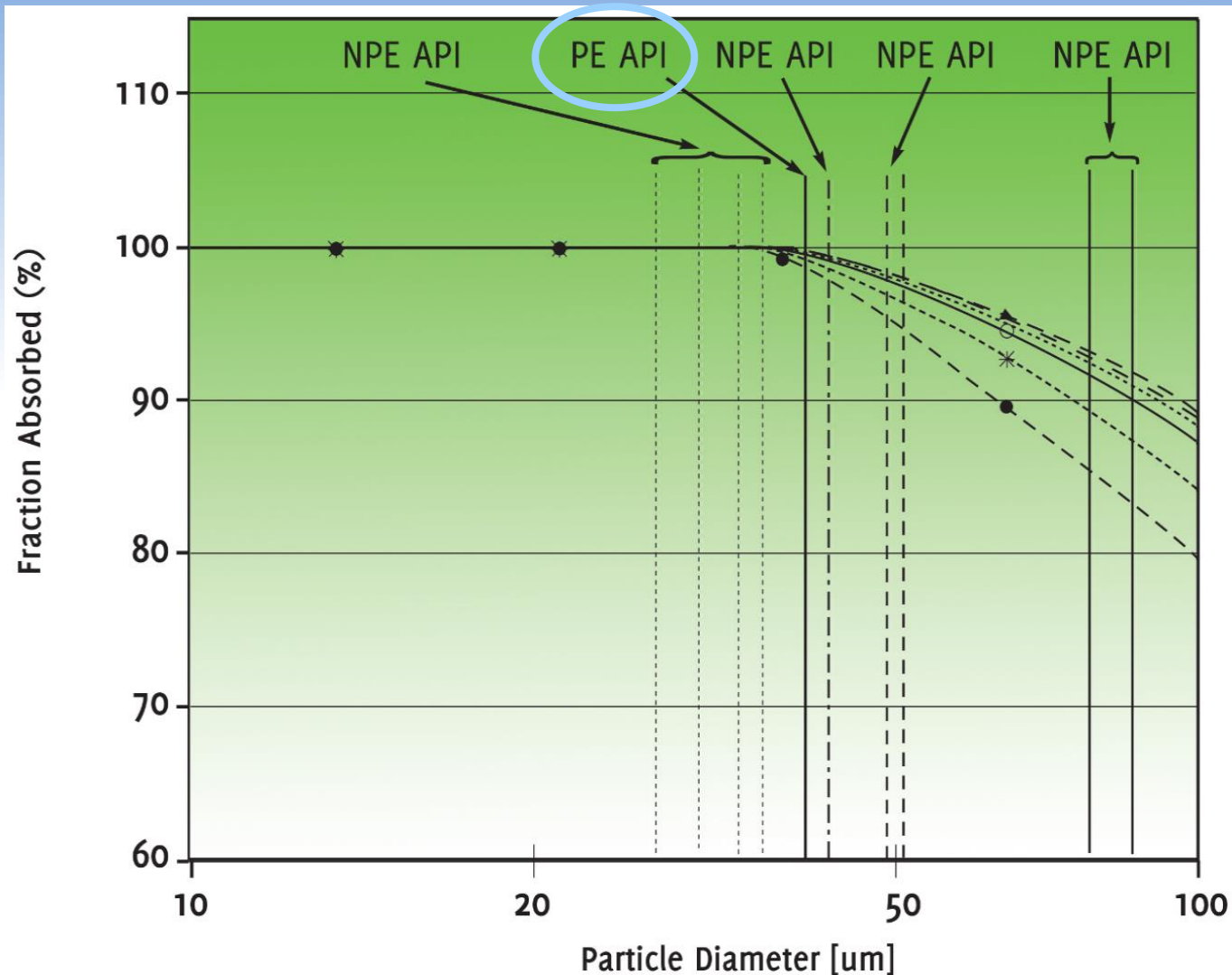
Baseline Model

- BCS Class IV drug
- Neutral compound
- Aqueous solubility = 10 µg/mL
- Significant solubilization by bile salts
- Intermediate lipophilicity
- No food effect



Same baseline absorption model does a good job of predicting the observed plasma concentration-time data across the three different doses of the NPE ("old") API lots

Effect of Particle size



- ▲ 10 mg
- △ 20 mg
- ◆ 50 mg
- ◇ 100 mg
- 200 mg
- * 500 mg
- 1000 mg

NPE (Non-Particle Engineered)
PE (Particle Engineered)

PSA was used to establish particle size specifications.

Results indicated that there would be small changes in Fa% until the largest particle sizes of the NPE API lots (> 30 - 40 μm) were reached *and* the dose exceeded 100 mg.

Population Simulations

Incorporate measured variability for physicochemical, formulation and PK parameters into Population Simulator

Population Simulator

File

Parameters

Clear All

Add All

Add Select

Set Defaults

Population

Set PEAR

Load Previous

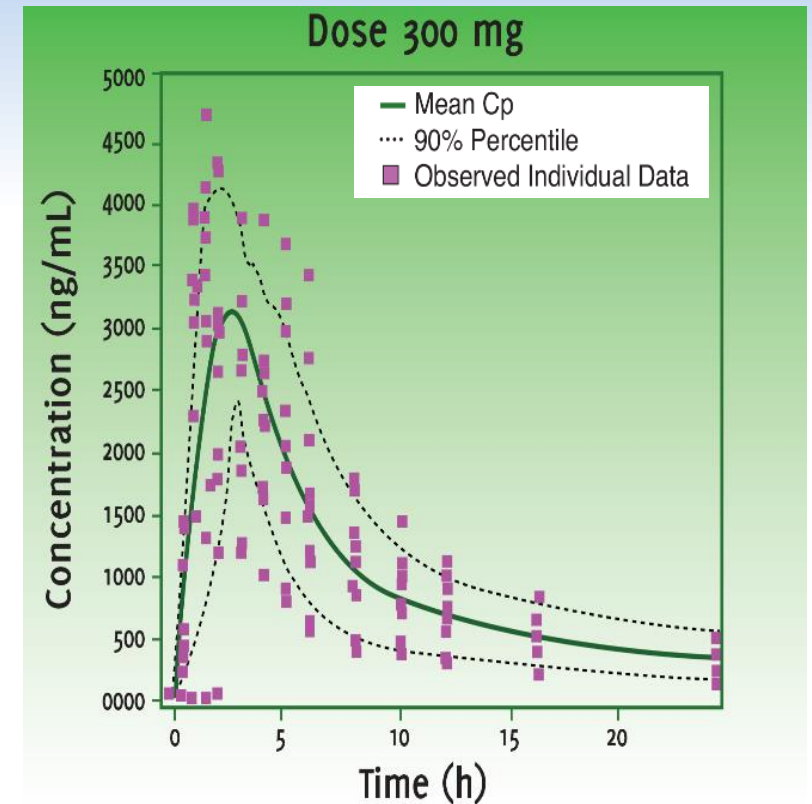
Create New

Parameter	Lower Limit	Mean Value	Upper Limit	CV%	Distribution
Dose of Valsartan (mg)	91.514	100	109.27	3	Log-Normal
Primary Permeability of Valsartan (c	0.2048	0.92	4.1328	65	Log-Normal
Particle Shape Factor of Valsartan	0.7513	1	1.331	10	Log-Normal
Mean Drug Particle Radius of Vals	18.783	25	33.275	10	Log-Normal
Precipitation Particle Radius of Vals	0.7513	1	1.331	10	Log-Normal
Precipitation Time of Valsartan (sec	676.18	900	1197.9	10	Log-Normal
Reference Solubility of Valsartan (n	0.0738	0.0982	0.1307	10	Log-Normal
Fraction Unbound in Enterocytes o	0.7513	1	1.331	10	Log-Normal
Oral Transit Time of Valsartan (h)	0.1878	0.25	0.3328	10	Log-Normal
Oral Cavity ASF Valsartan	0.7513	1	1.331	10	Log-Normal
Duodenum ASF Valsartan	2.1011	2.7965	3.7221	10	Log-Normal
Jejunum 1 ASF Valsartan	2.0672	2.7514	3.6621	10	Log-Normal
Jejunum 2 ASF Valsartan	2.0506	2.7294	3.6328	10	Log-Normal
Ileum 1 ASF Valsartan	2.0273	2.6983	3.5914	10	Log-Normal
Ileum 2 ASF Valsartan	1.988	2.6461	3.522	10	Log-Normal
Ileum 3 ASF Valsartan	1.9416	2.5843	3.4396	10	Log-Normal
Caecum ASF Valsartan	0.0797	0.1061	0.1412	10	Log-Normal
Asc Colon ASF Valsartan	0.1551	0.2064	0.2747	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	7.5131	10	13.31	10	Log-Normal
Fraction of SI fluid volume in fasted	30.053	40	53.24	10	Log-Normal
Small Intestine Length (cm)	230.01	306.14	407.47	10	Log-Normal
Caecum Length (cm)	9.9118	13.193	17.559	10	Log-Normal
Colon Length (cm)	20.772	27.648	36.799	10	Log-Normal
Stomach Volume (mL)	34.981	46.56	61.972	10	Log-Normal
Small Intestine Radius (cm)	0.7513	1	1.331	10	Log-Normal
Caecum Radius (cm)	2.5433	3.3851	4.5056	10	Log-Normal
Colon Radius (cm)	1.8086	2.4073	3.2041	10	Log-Normal
Stomach Transit Time (h)	0.1447	0.25	0.432	20	Log-Normal
Small Intestine Transit Time (h)	1.857	3.2088	5.5448	20	Log-Normal

Number of Output Data Points 300

OK Cancel

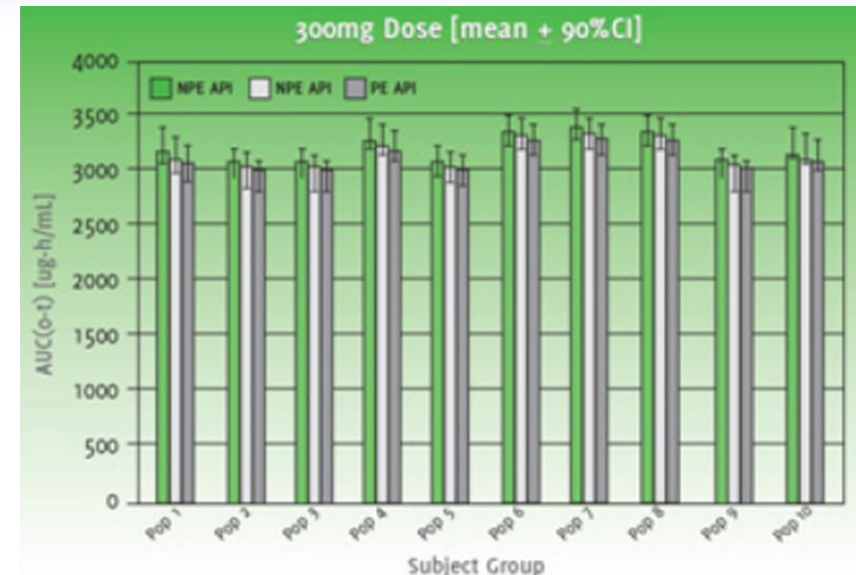
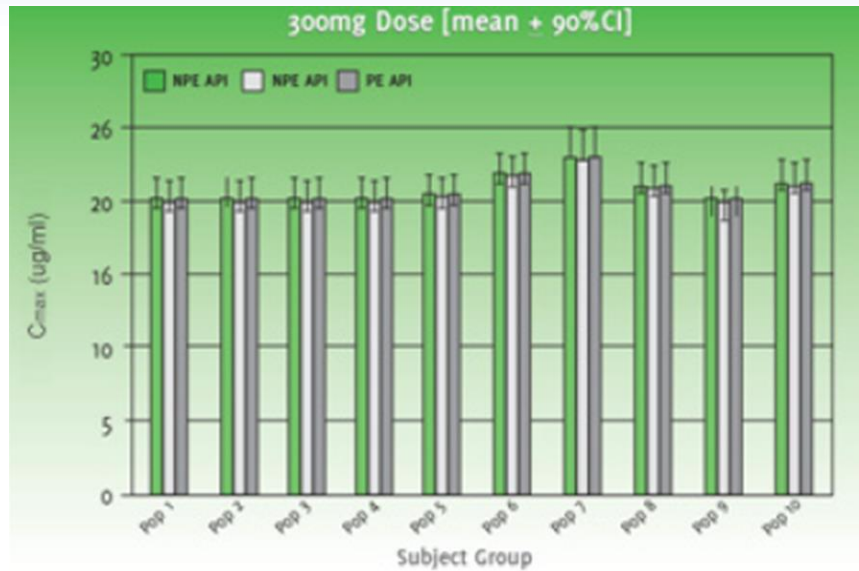
Capture observed variability from existing clinical PK studies



Virtual Bioequivalence

Crossover studies simulations for **10 different populations**, each with **25 virtual subjects**, were run to predict bioequivalence

100% passing ratios for C_{max} and AUC were predicted (within the 80-125% limits) between the “new” and “old” API lots (up to 40 µm)



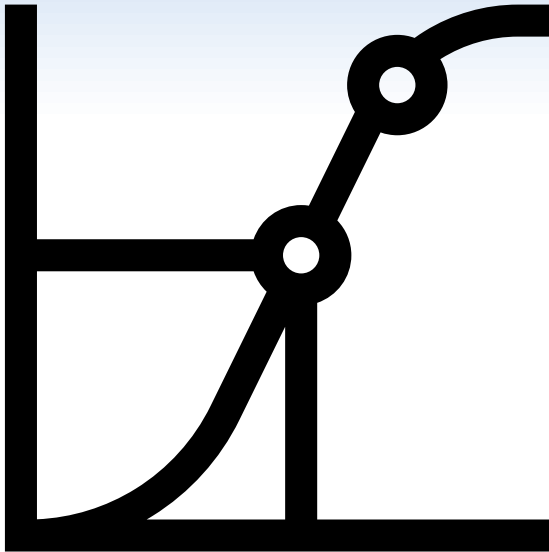
Conclusion

- A mechanistic, PBPK model validated using GastroPlus across three dose levels using in vivo data collected from tablets manufactured with non-particle engineered API.
- Parameter sensitivity analysis showed that mean particle size (D50) would be the main property that determines whether formulations are likely to be bioequivalent, regardless of dose.
- Virtual bioequivalence trial simulations showed the C_{max} and AUC values would be bioequivalent between the tablets manufactured with NPE vs. PE API, up to 40 µm particle size, regardless of the dose.
- Regulatory agencies approved the sponsor's biowaiver application ★

IR: dissolution

Z-factor Model

In Vitro Dissolution
Profiles



Fit of Z-factor
parameter



In Vivo PK
Prediction



Case Study

Virtual clinical trial to predict BE between a test and reference formulations for a BCS 2 compound

Objectives

Context:

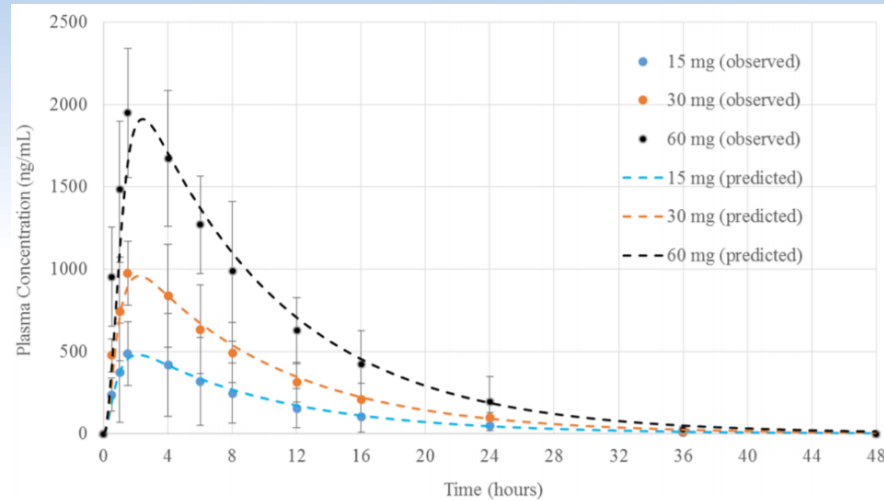
- Dissolution rate limited absorption
- Multiple test formulations were created

M&S to run virtual BE in order to pick the correct test formulation(s):

- In vitro dissolution profiles available for multiple strengths of the reference formulation
- Corresponding observed PK profiles exist
- In vitro dissolution profiles available for all test formulations
- Z-factor, Johnson and effective PSD models were tested

Model Predictions

Z factor model withing GastroPlus provided the best IVIVR results for all doses of the reference formulation



Validation of the Z-factor method to predict in vivo PK based on in vitro dissolution profiles
→ Selection of the test formulation based on 42 virtual BE

Predicted and observed pharmacokinetic parameters, GMR and 90% CI for IR formulation of compound B for pivotal BE study in fasted state.

	Observed			Simulated		
	AUC ₀₋₄₈ (ng/mL*hr)	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₄₈ (ng/mL*h)	C _{max} (ng/mL)	T _{max} (hr)
Reference	14020	1388	2.2	14193	1412	2.6
Test	14441	1360	2.1	14931	1442	2.5
	AUC		C _{max}	AUC		C _{max}
GMR (T/R)	1.03		0.98	1.05		1.02
90% CI	0.97–1.09		0.92–1.06	0.98–1.06		0.93–1.04



Observed results of the pivotal BE study demonstrate the model could predicted GMR and 90%CI

Case Study

Investigation of warfarin bioequivalence by US. FDA

Objectives

Context:

- Warfarin is a weak acid with $pK_a = 5.05$
- Previous work demonstrated warfarin sodium tablets could undergo a change in crystalline form after brief exposures to higher temperature and humidity
- Clinical significance (in terms of drug bioavailability) of this product quality variation was unknown

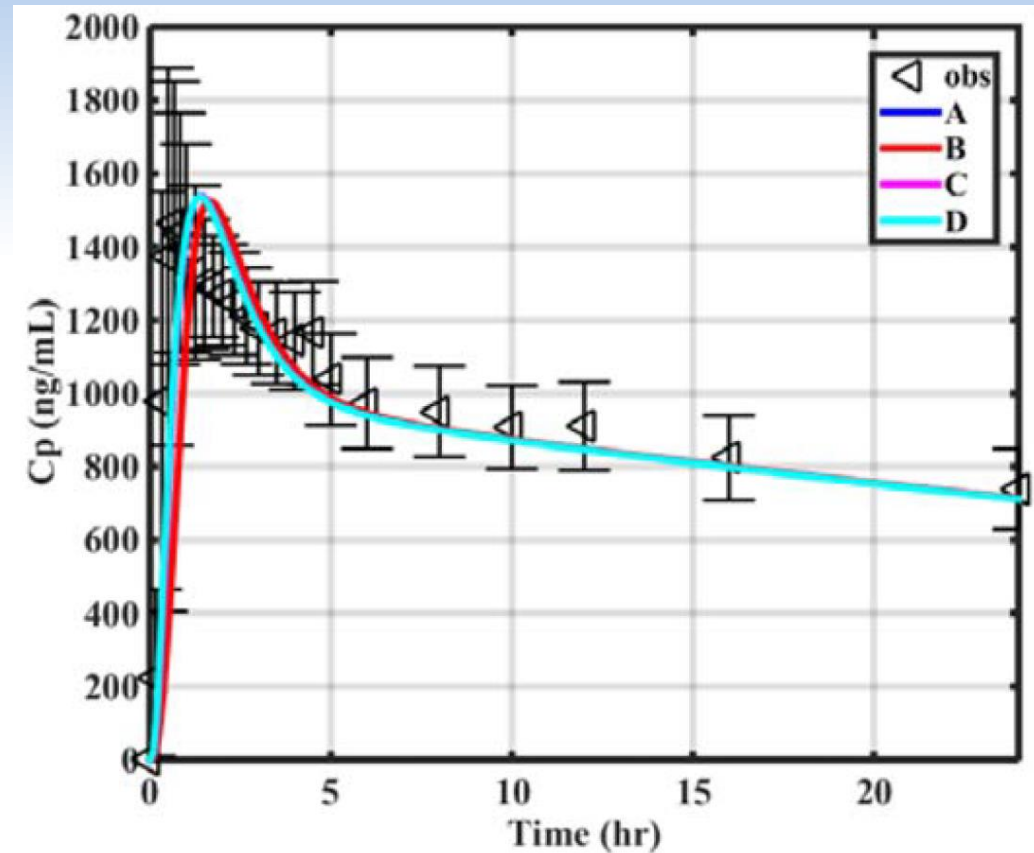
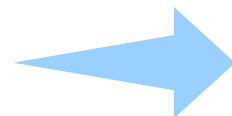
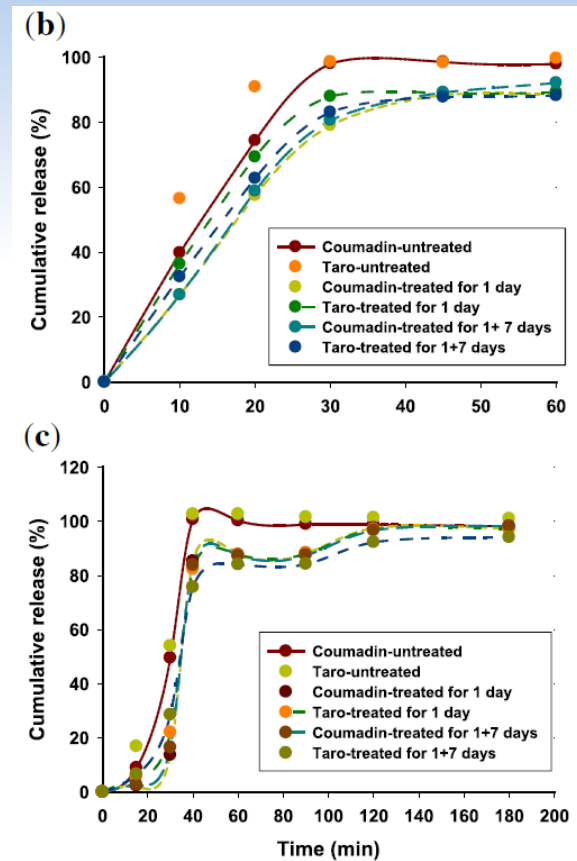
M&S and clinical study to assess the impact of product quality change on its in vivo performance

2 formulations (Coumadin & Taro) and 3 conditions:

- Untreated: intact drug products
- stored in 40°C/75% relative humidity (RH) for 24 hours
- stored in 40°C /75% RH for 24 hours plus in 25°C /60% RH for 7 days

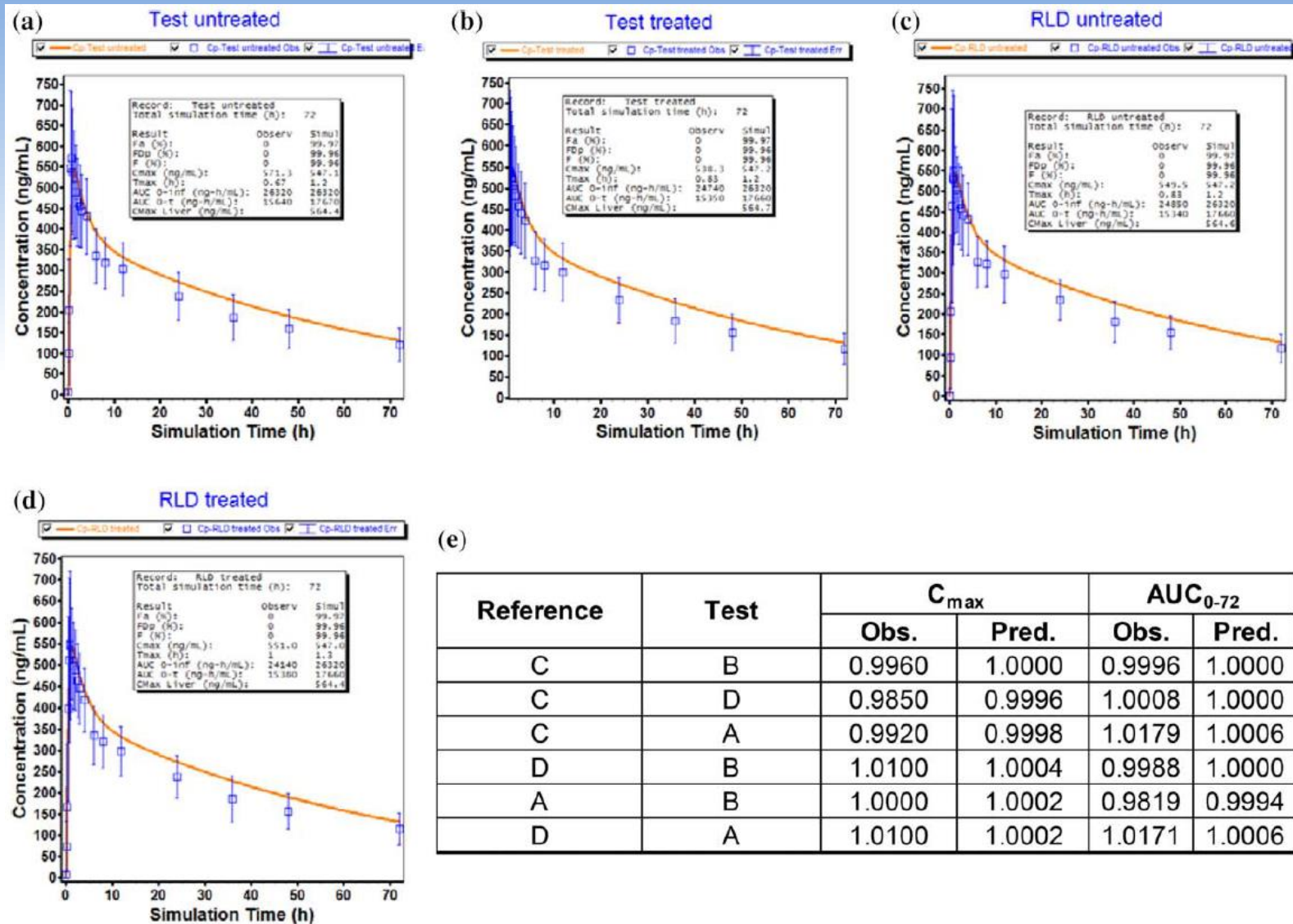
Model Predictions

Z factor model within GastroPlus was used to link in vitro dissolution data to in vivo PK profiles



In vitro dissolution in pH 4.5 (top)
and two stage buffer (bottom)

Virtual and Clinical Bioequivalence



PE between
reference and
test

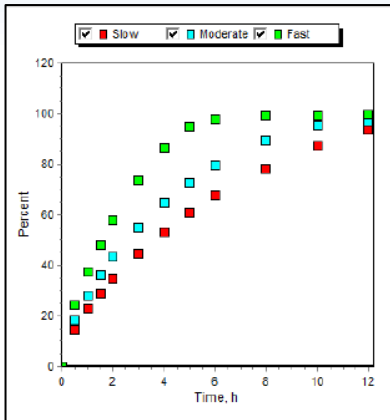


MR Formulation

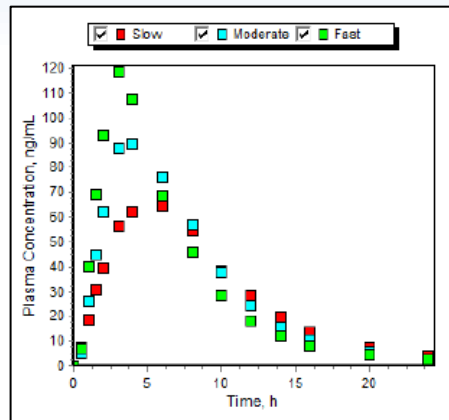
IVIVC

An IVIVC is a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response

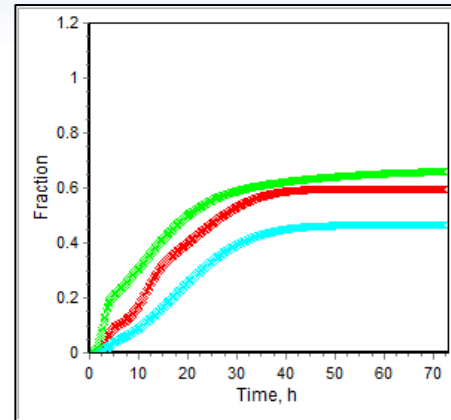
In vitro release



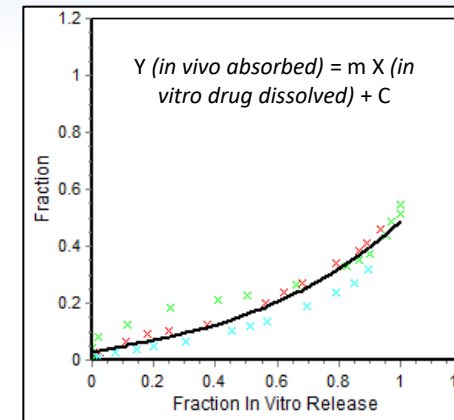
In vivo PK



Deconvolution



Convolution



Evaluation

- Internal/external validation
- Cmax and AUC % criteria

Once IVIVC is validated drug PK profiles can be predicted based on in vitro dissolution only



Commentary

Theme: Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development
Guest Editors: Marilyn N. Martinez, Sandra Suarez, and Andreas Abend

PBPK Absorption Modeling: Establishing the *In Vitro*–*In Vivo* Link—Industry Perspective

**Cordula Stillhart,¹ Xavier Pepin,² Christophe Tistaert,³ David Good,⁴ An Van Den Bergh,⁵
Neil Parrott,⁶ and Filippou Kesisoglou^{7,8}**

Case Study

IVIVC for MR formulation for a BCS III
candidate drug development

Objectives

Context:

- MK-0941 presents regional dependent absorption with reduced bioavailability from the colon compared to oral administration
- Two types of formulations, matrix tablets and multiparticulates in capsules

M&S to establish both traditional and mechanistic IVIVCs:

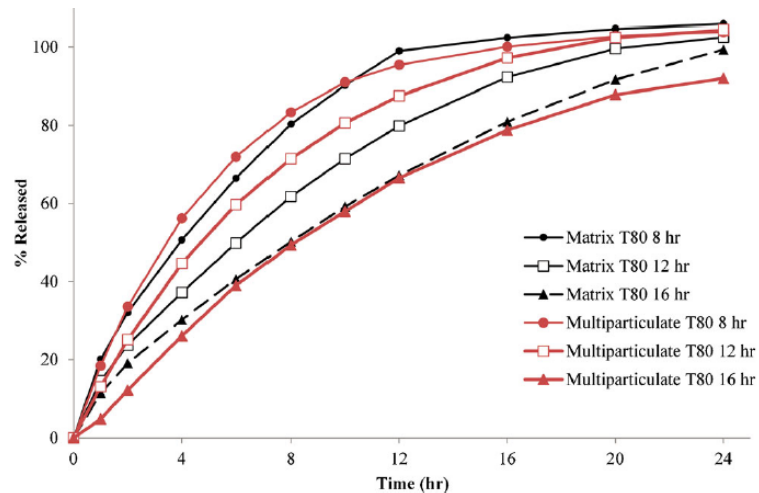


Fig. 1. Average ($n=6$) dissolution profiles for matrix and multiparticulate MK-0941 formulations used for IVIVC model development

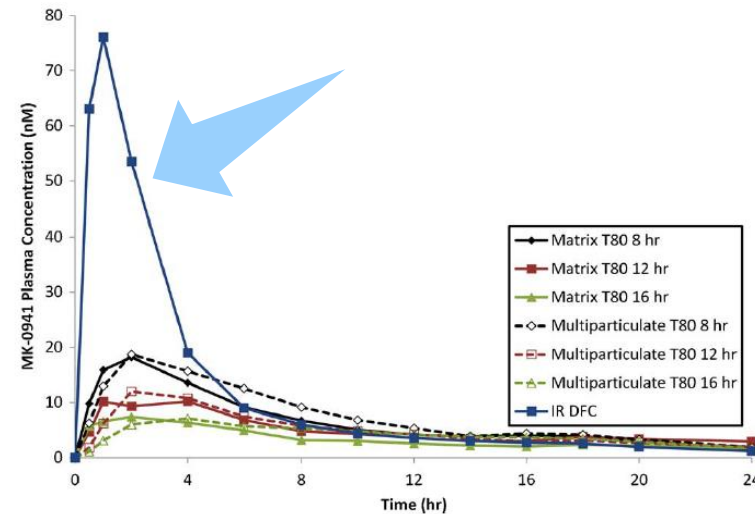


Fig. 2. Mean ($n=16$) plasma concentration vs. time profiles for MK-0941 IR and ER formulations

Mechanistic IVIVC

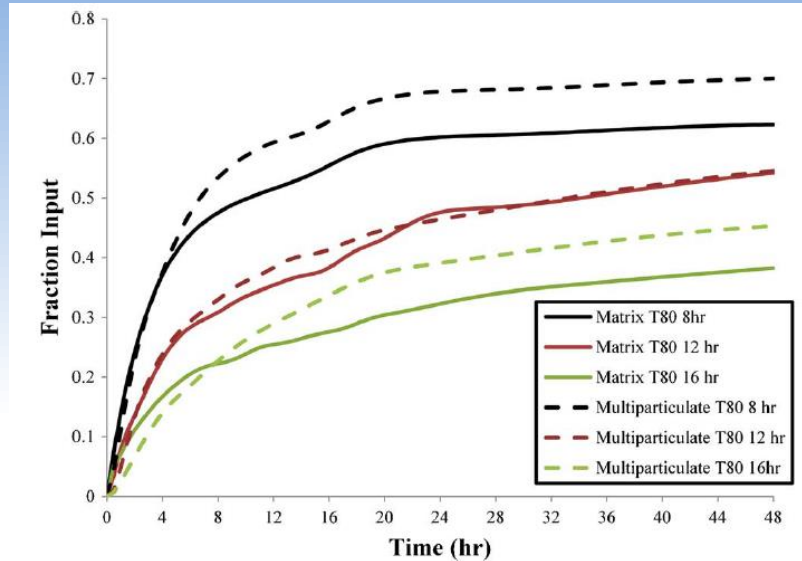


Fig. 3. Average fraction input vs. time profiles for MK-0941 ER formulations estimated by deconvolution



Correlation phase between the observed in vitro and predicted in vivo dissolution profiles

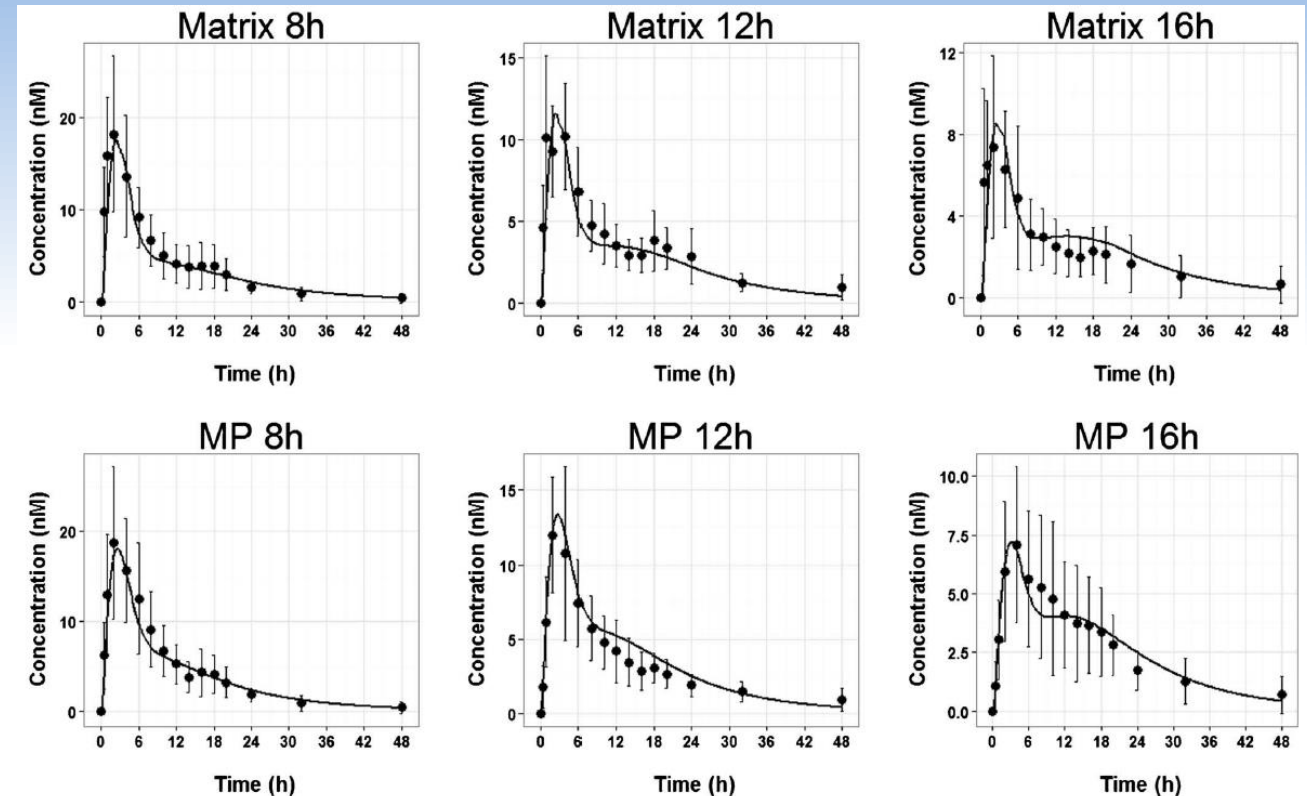
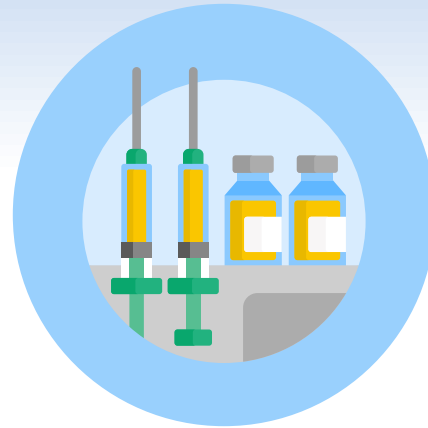


Fig. 6. Absorption PBPK IVIVC model predicted (lines) vs. observed (squares, mean \pm SD) plasma concentration vs. time profiles for MK-0941 ER formulation

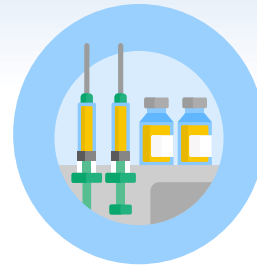
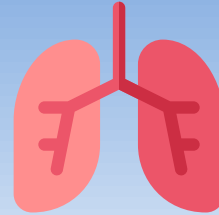


Other routes of administration

Ocular



Pulmonary



Dermal



Oral Cavity



Intra-muscular



Intra-articular

Conclusions

- Mechanistic absorption modeling can be used to predict in vivo PK data based on in vitro dissolution profiles for oral formulations (IR and MR)
- GastroPlus is a mechanistically based simulation software package that is constantly evolving to include new knowledge and dosage routes
- To increase the likelihood of a successful IVIVR/IVIVC, a biorelevant vitro dissolution method is preferred



Thank you!