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

Maxime Le Merdy

Senior Scientist, Simulations Plus

APS

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

The Academy of Pharmaceutical Sciences

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Simulations Plus – Who We Are…

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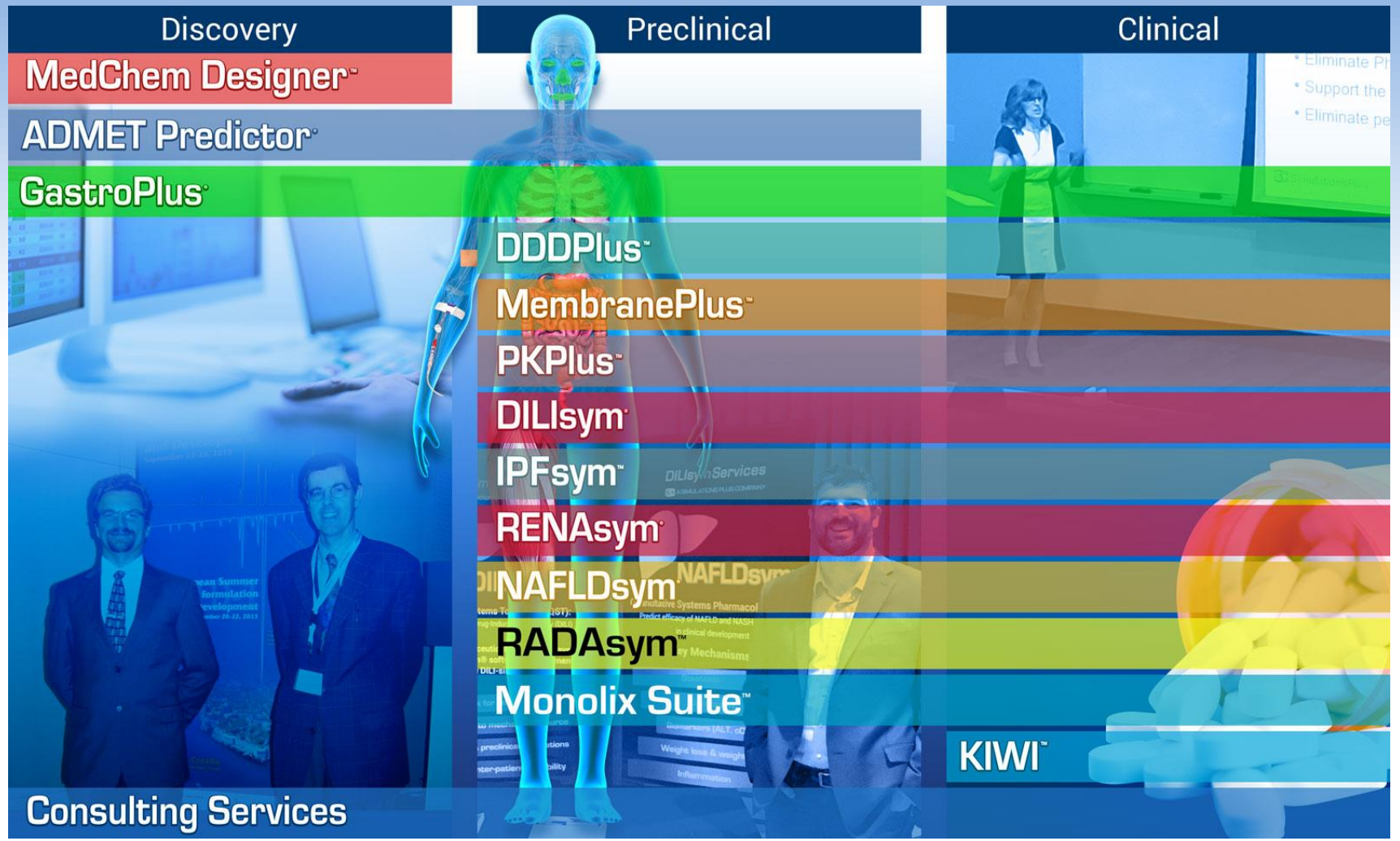
Simulations Plus – Technology Offerings



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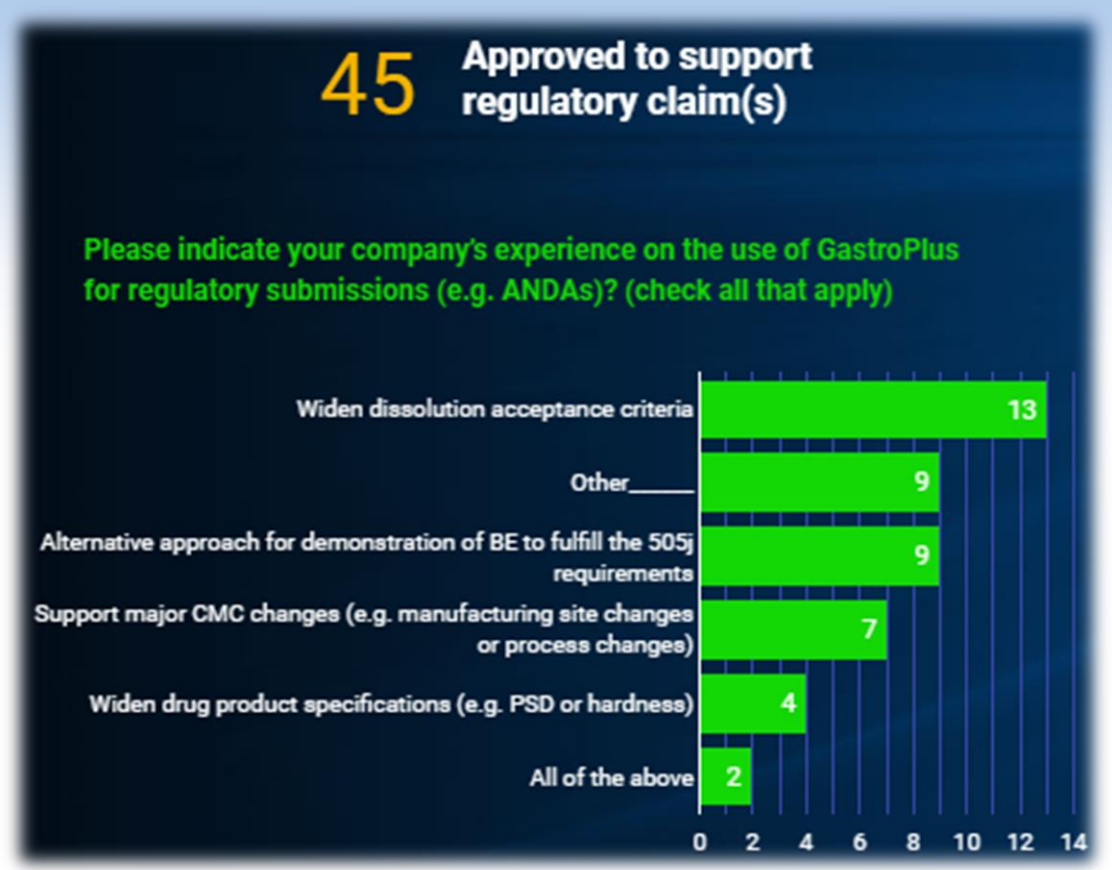
GastroPlus®

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



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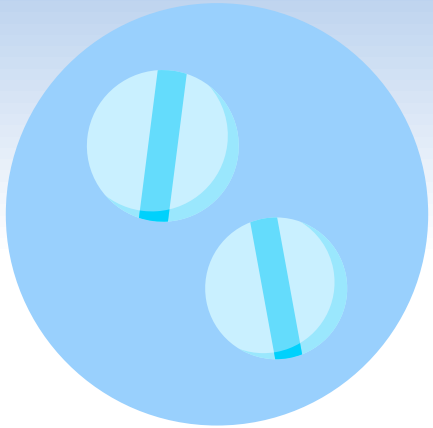
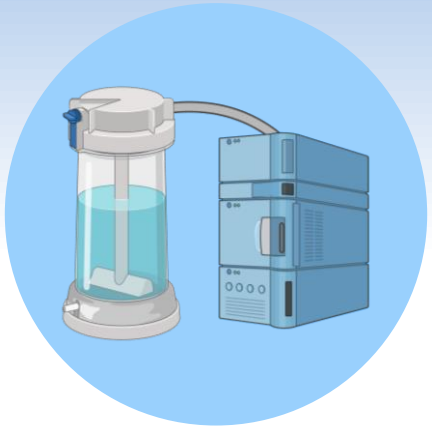
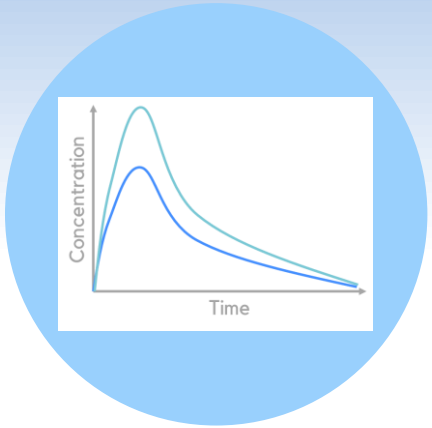
The goal: predict *In Vivo* PK



Formulation

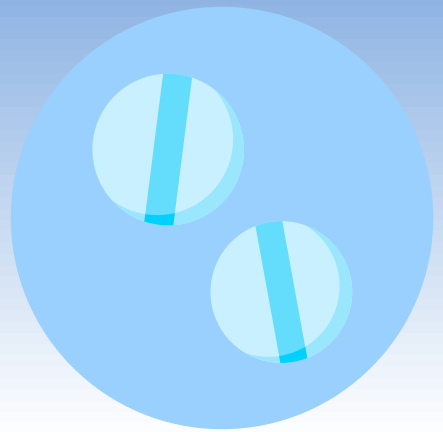


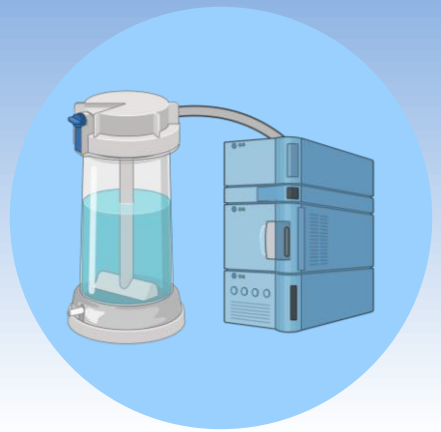
In Vitro

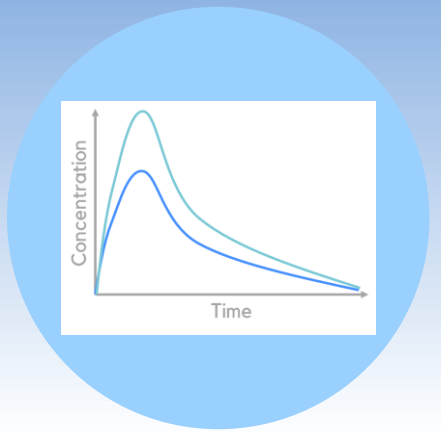


In Vivo

The goal: predict *In Vivo* PK







Formulation → ***In Vitro*** → ***In Vivo***

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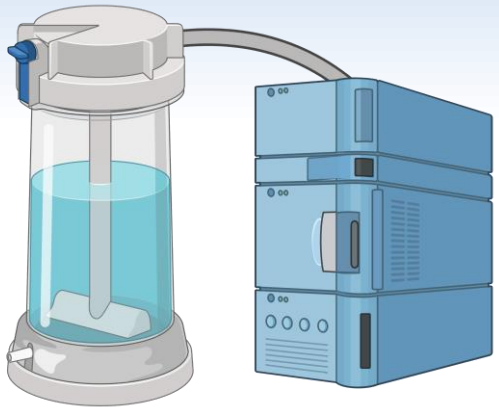
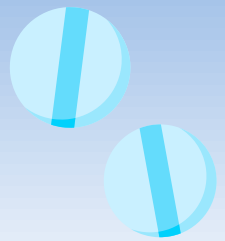
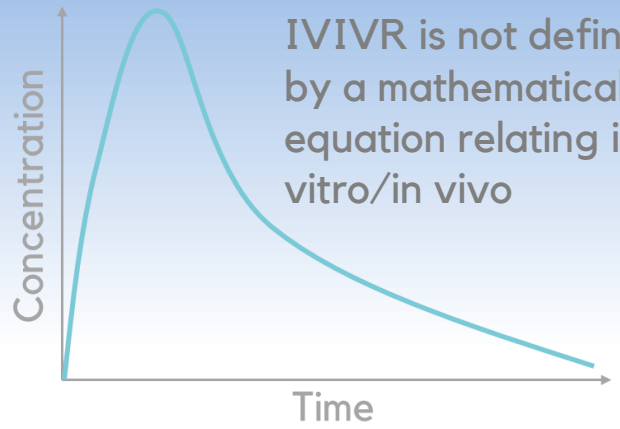
Predict *In Vivo* PK: framework



Immediate release



PBBM –IVIV Relationship

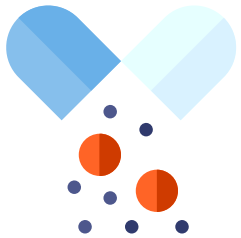


IVIVR is not defined by a mathematical equation relating in vitro/in vivo

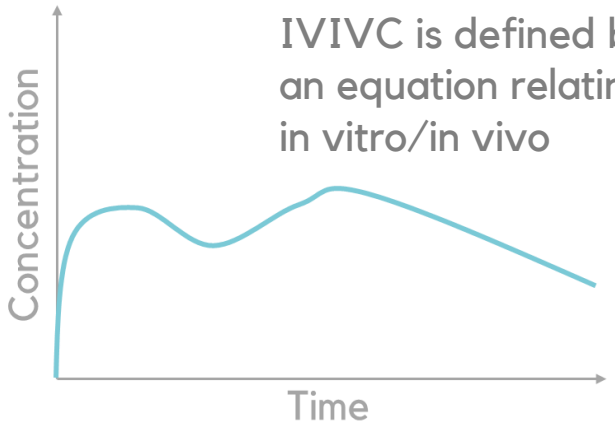
Virtual Bioequivalence

CRDS

Modified release

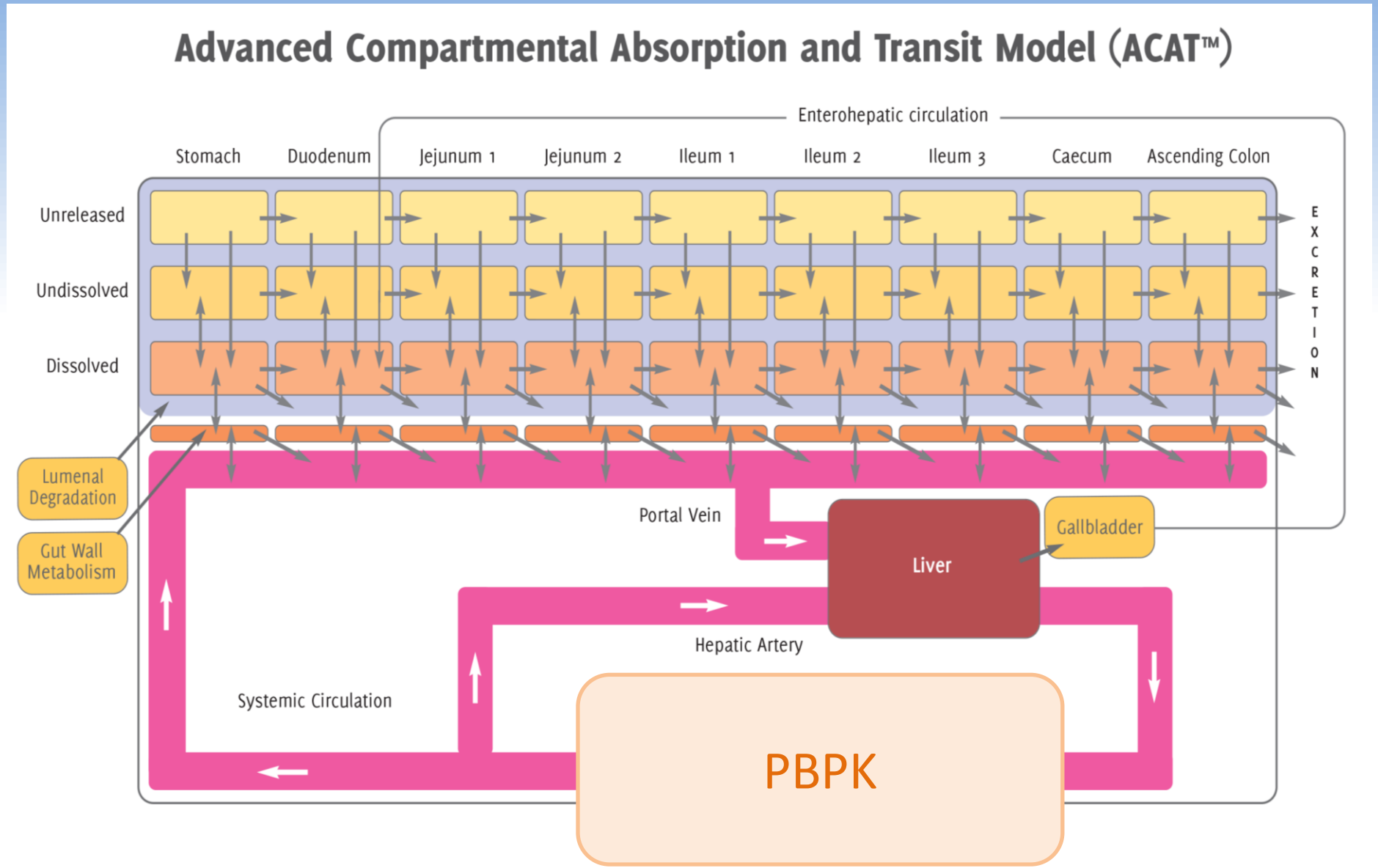


PBBM –IVIV Correlation



IVIVC is defined by an equation relating in vitro/in vivo

PBBM & GastroPlus



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:

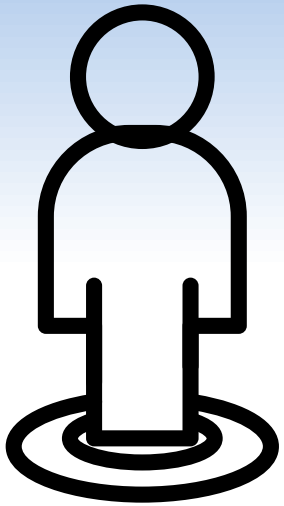
  Gut physiology parameters

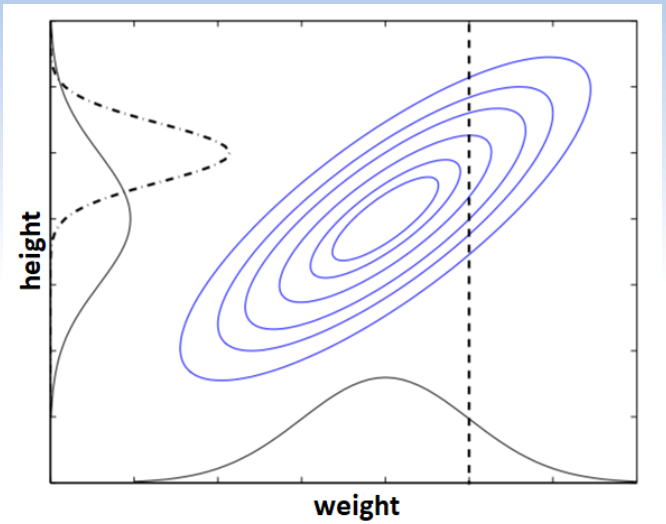
  Pharmacokinetic parameters

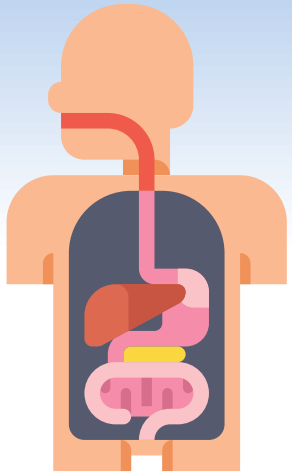
  PBPK parameters

  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

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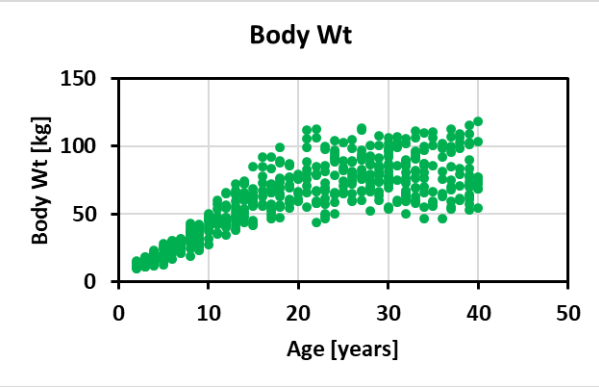
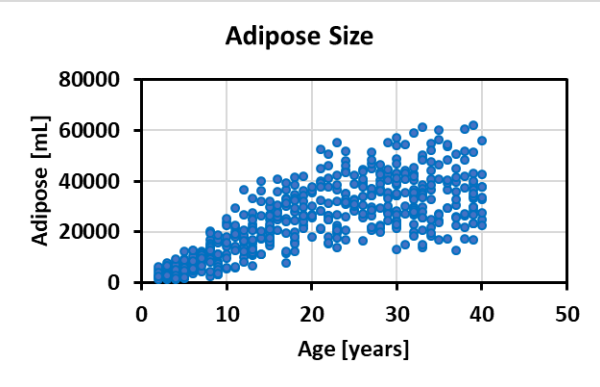
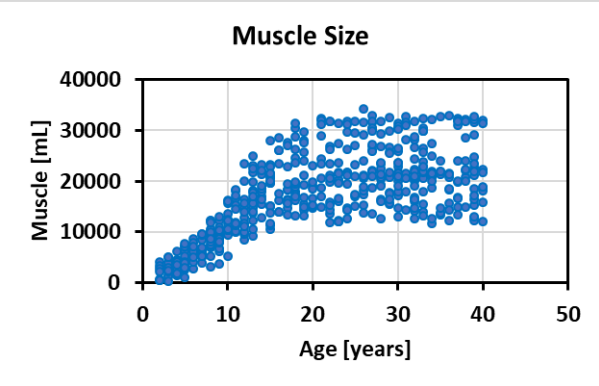
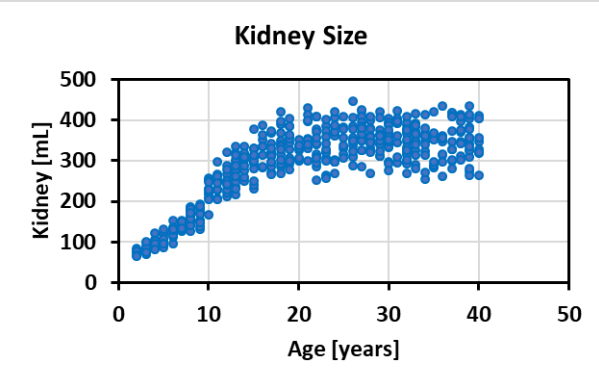
Virtual BE & GastroPlus

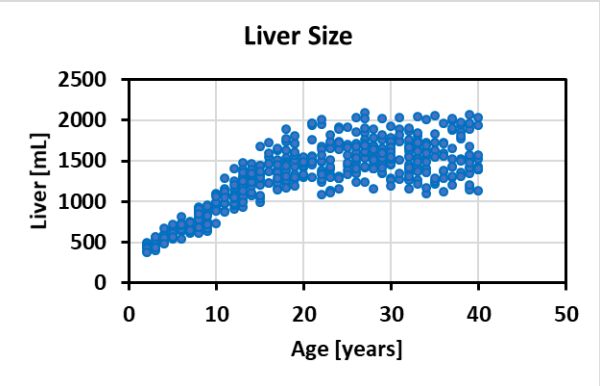
Population of 500 subjects; 2-40 years old; 50% males;
body weight from 60-140% of typical weight, BMI up to 32

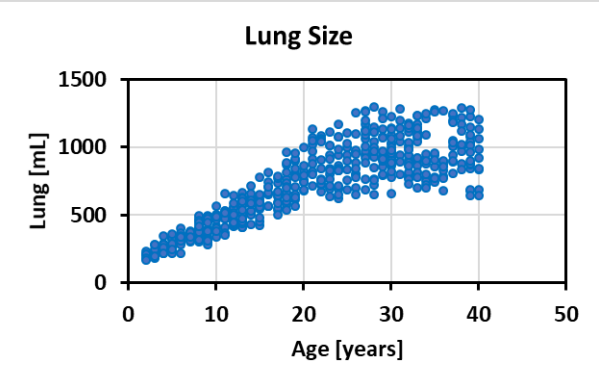












- Can generate wider range of body weights (more realistic general population)
- Includes variability on body heights
- Have more options for creating populations of subjects

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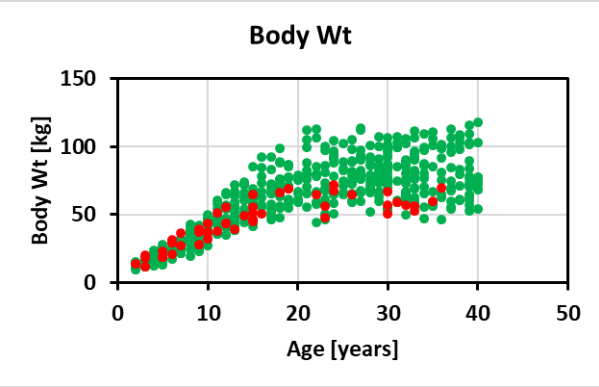
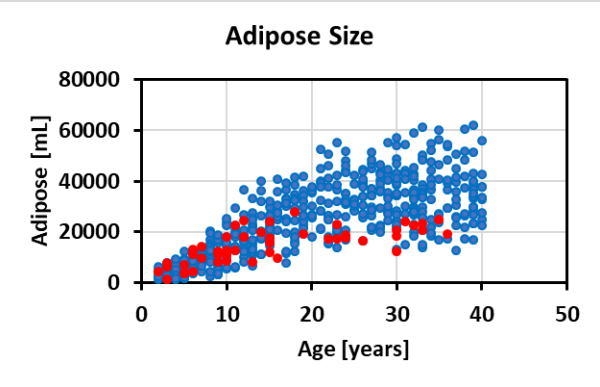
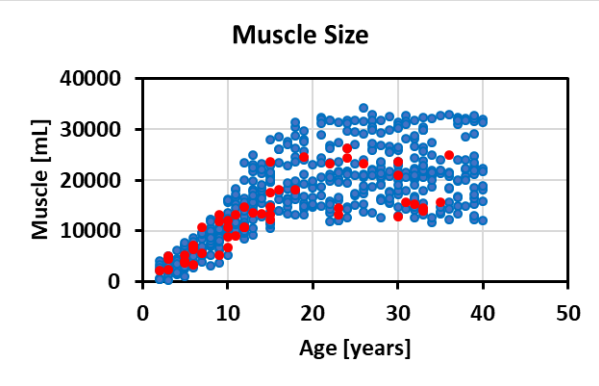
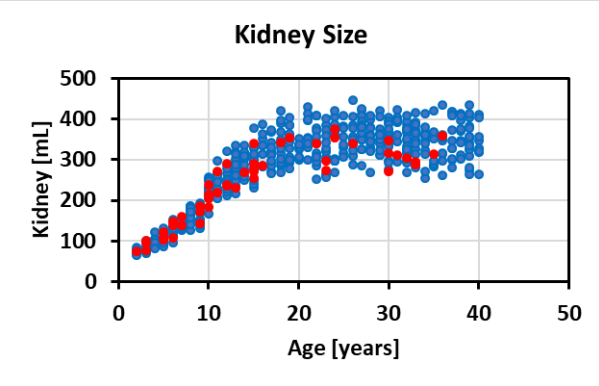
Virtual BE & GastroPlus

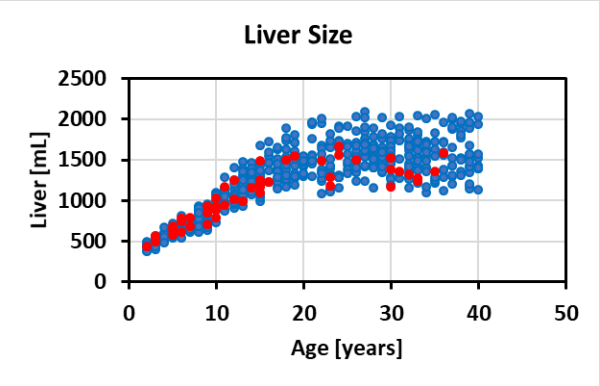
Population of 50 subjects; 2-40 years old; 50% males;
body weight from 60-140% of typical weight, BMI up to 21

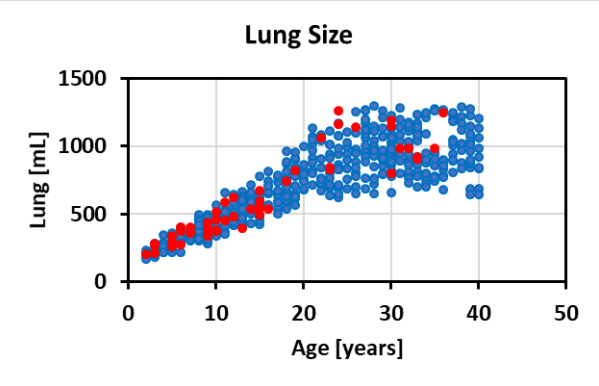












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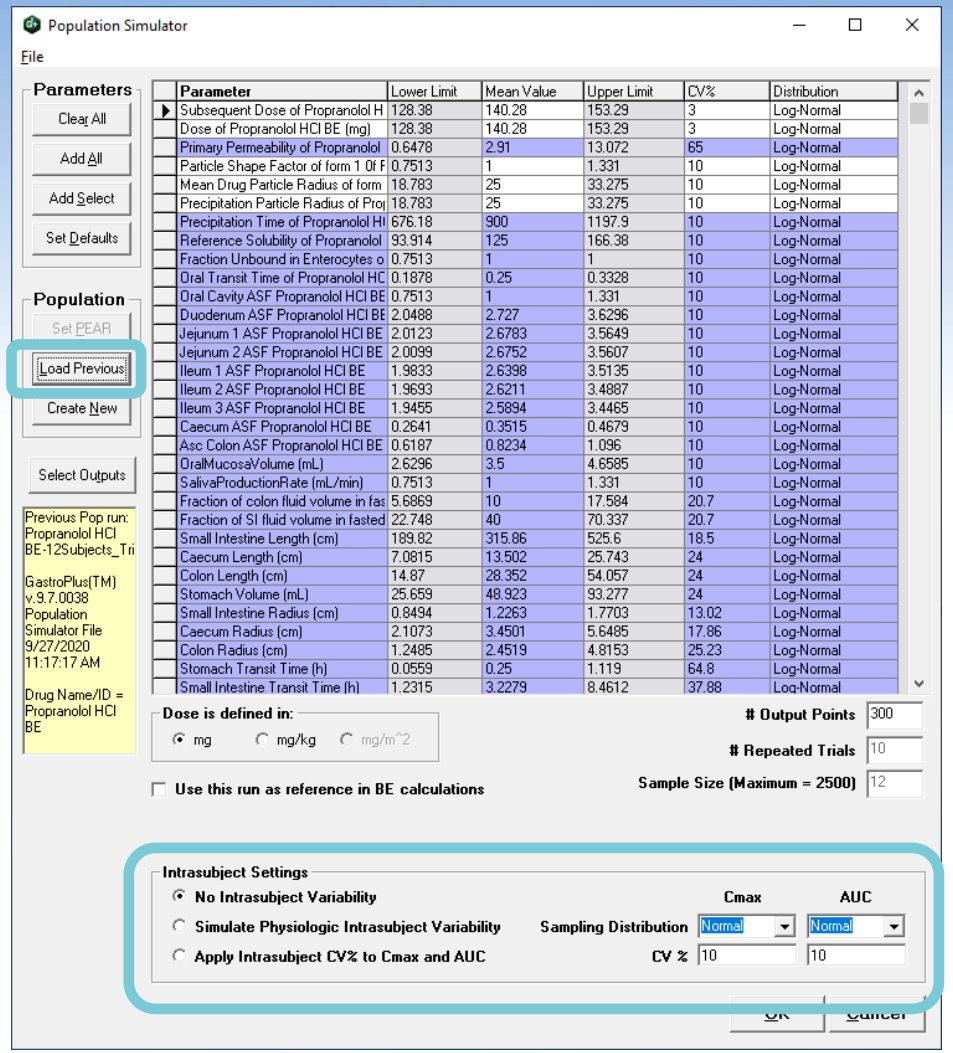
Intra-subject variability



No intrasubject variability

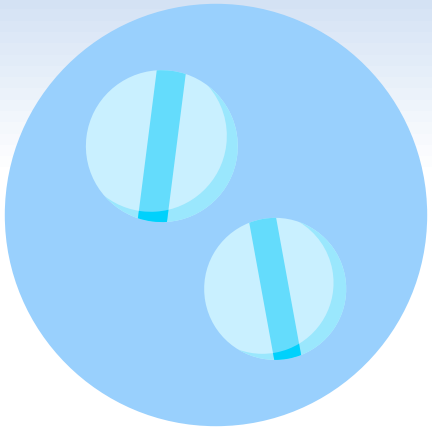
- same subject parameters as in previous versions of GastroPlus

Intrasubject variability on input parameters

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

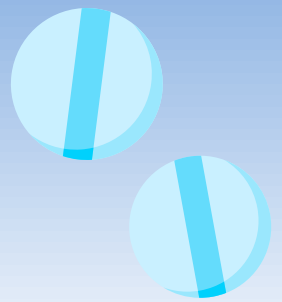
Intrasubject variability on the resulting C_{max} and AUCs

- 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

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

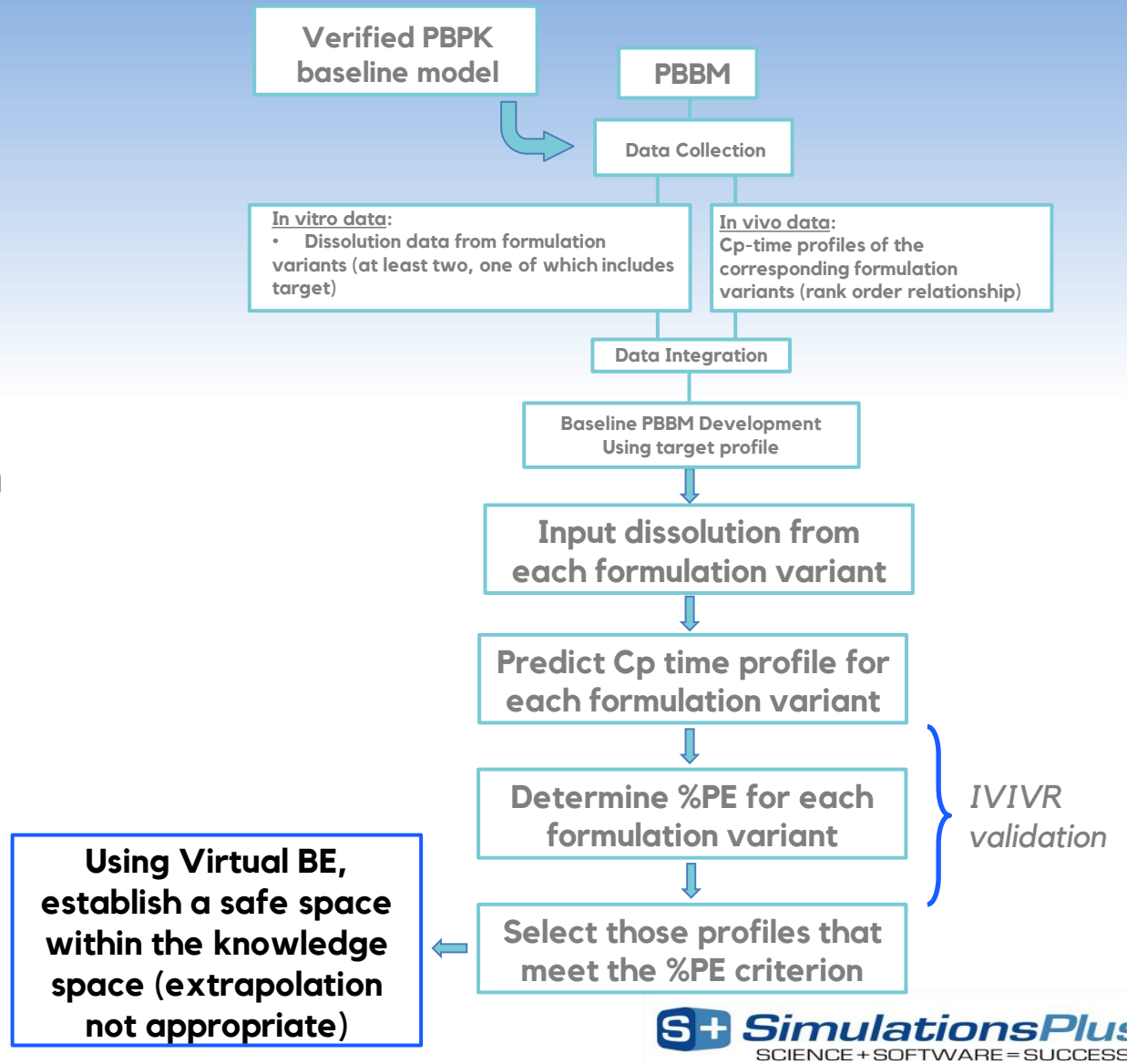
z represents $\frac{3D_w}{\rho r T}$ and is determined by fitting to in vitro dissolution data

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**



CMA: critical material attribute
CPP: critical process parameter
CFV: critical formulation variable

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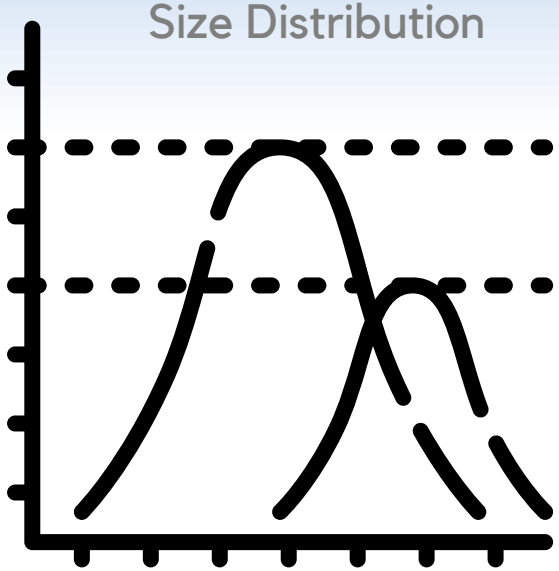
IR: dissolution

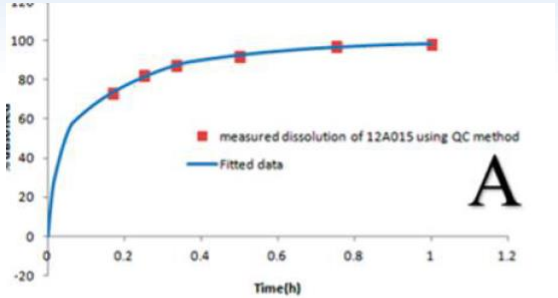
Johnson Model

In Vitro Particle Size Distribution



In Vivo PK Prediction

Fitted Particle Size Distribution



Radius (um)	% w/w
10	13.05
20	30.36
30	1.67
50	25.22
100	20.26
200	8.36
300	1.09

Pepin et al. 2016

Case Study

Crossover trials to show Bioequivalence after manufacturing changes

Tistaert, C. AAPS Annual Meeting 2015, Orlando, FL

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Objectives

Context:

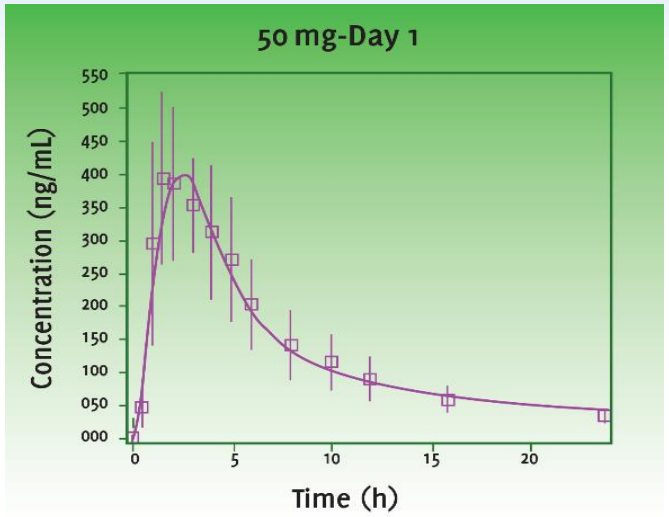
- Post-approval, sponsor's manufacturing process changes resulted in different particle size distributions for new lots: Inline milling step added to crystallization process (PE)

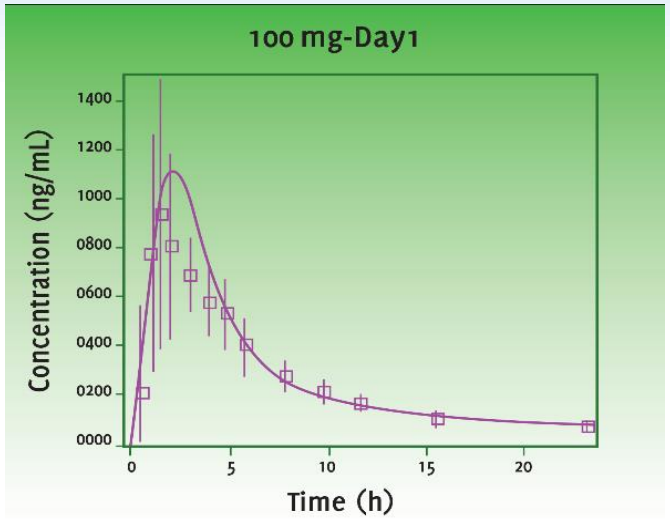
Modeling and Simulations (M&S) to request a biowaiver by:

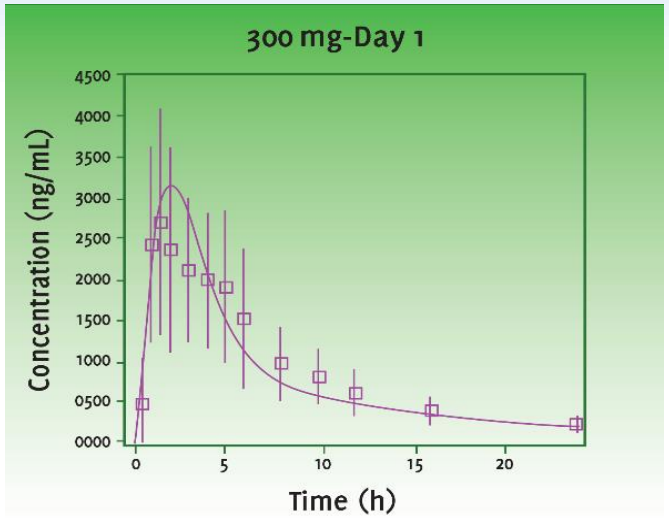
- Assessing the effects of changes in particle size distribution of the active pharmaceutical ingredient (API) on its oral bioavailability
- Predicting the virtual bioequivalence between the "new" and "old" API lots

Baseline Model

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

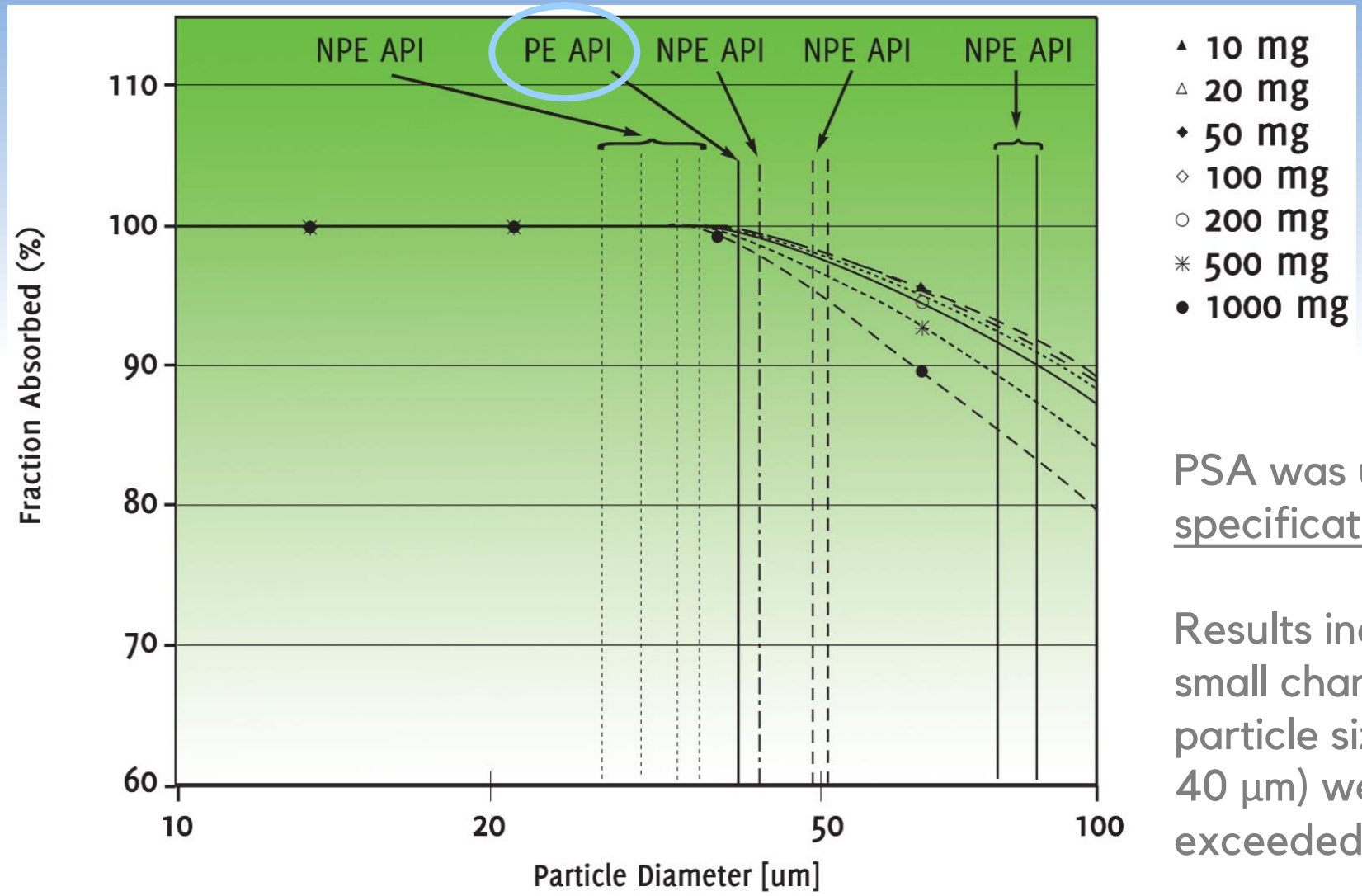






Same baseline absorption model does a good job of predicting the observed plasma concentration-time data across the three different doses of the NPE ("old") API lots

Effect of Particle size



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.

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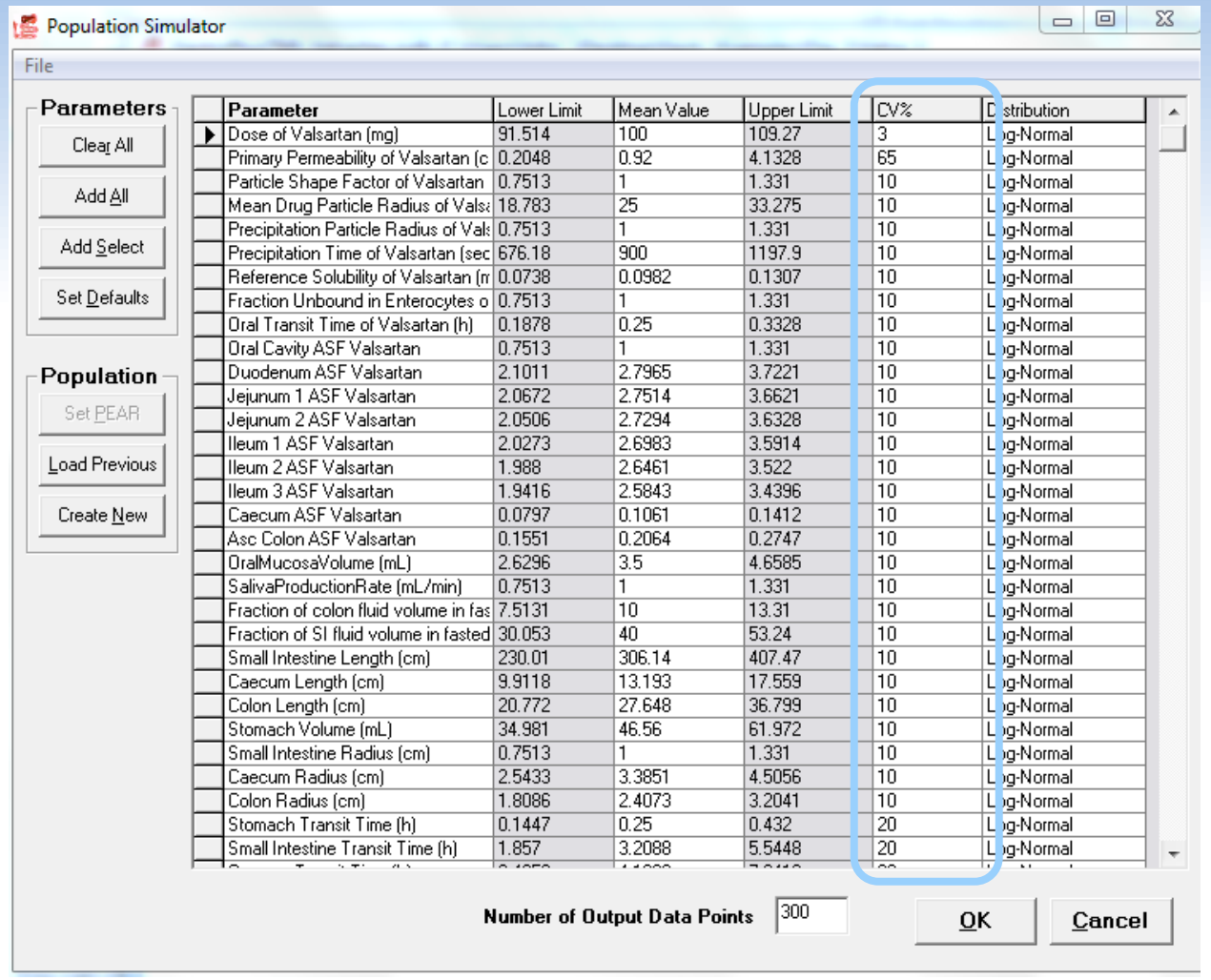
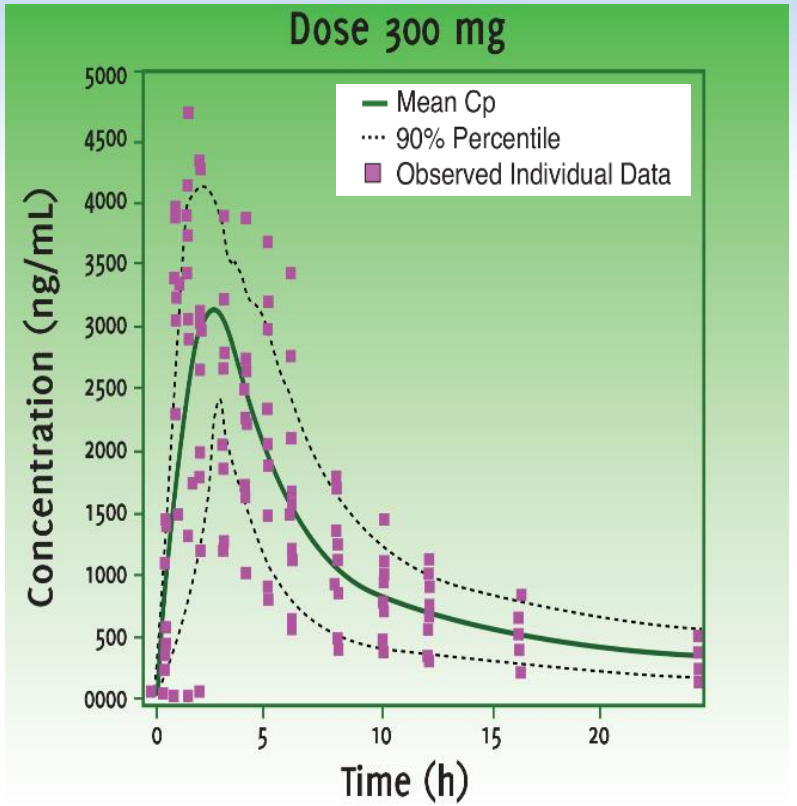
Population Simulations

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



Capture observed variability from existing clinical PK studies



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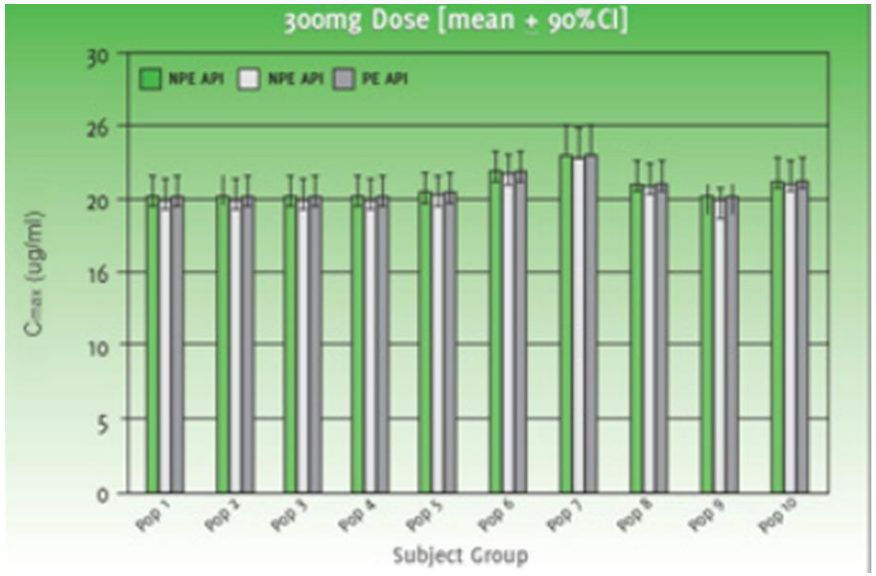
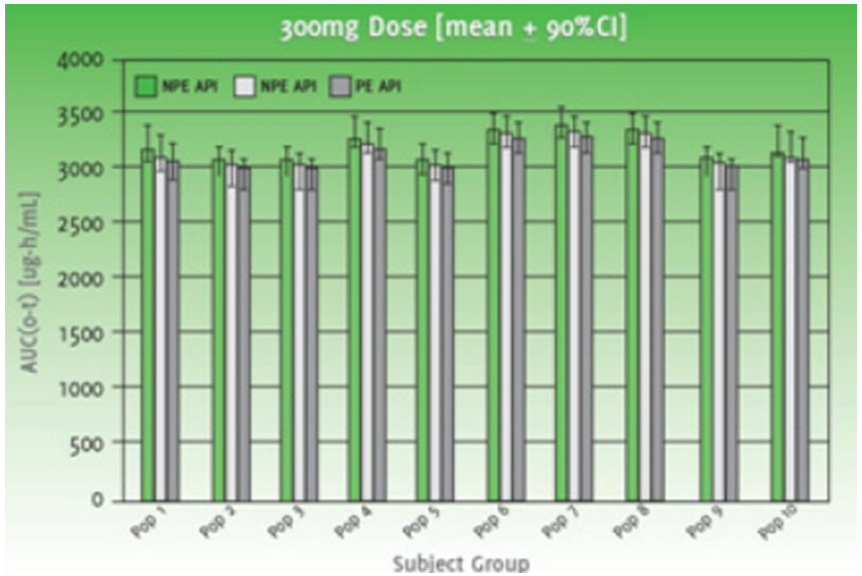
Virtual Bioequivalence

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

100% passing ratios for Cmax and AUC were predicted (within the 80-125% limits) between the "new" and "old" API lots (up to 40 μm)





SimulationsPlus
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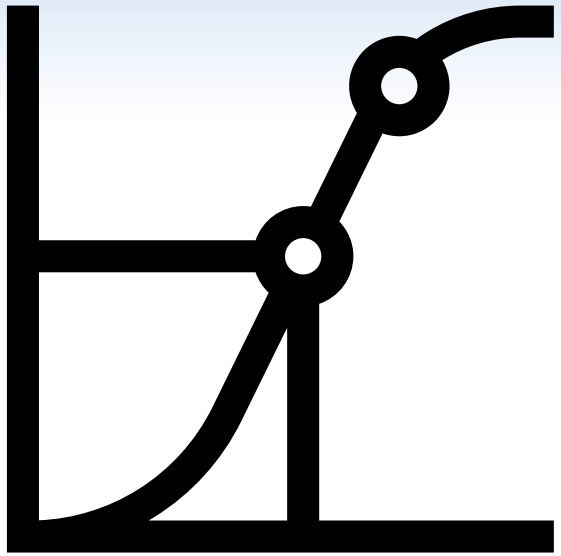
Conclusion

- 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 Cmax 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



In Vivo PK Prediction

Fit of Z-factor parameter

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Case Study

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

Mitra, European Journal of Pharmaceutics and Biopharmaceutics 2019

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Objectives

Context:

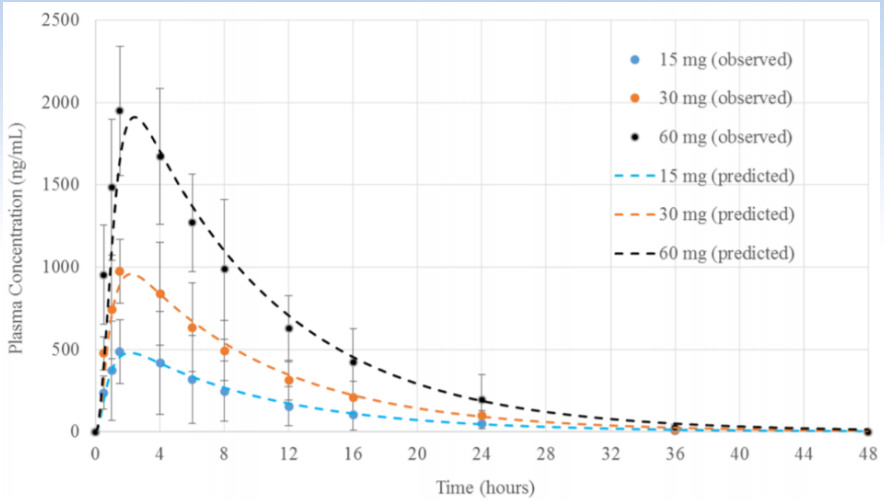
- Dissolution rate limited absorption
- Multiple test formulations were created

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
- Coresponding 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



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	

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

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

Zhang, CPT:PSP 2017

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Objectives

Context:

- Warfarin is a weak acid with pKa = 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

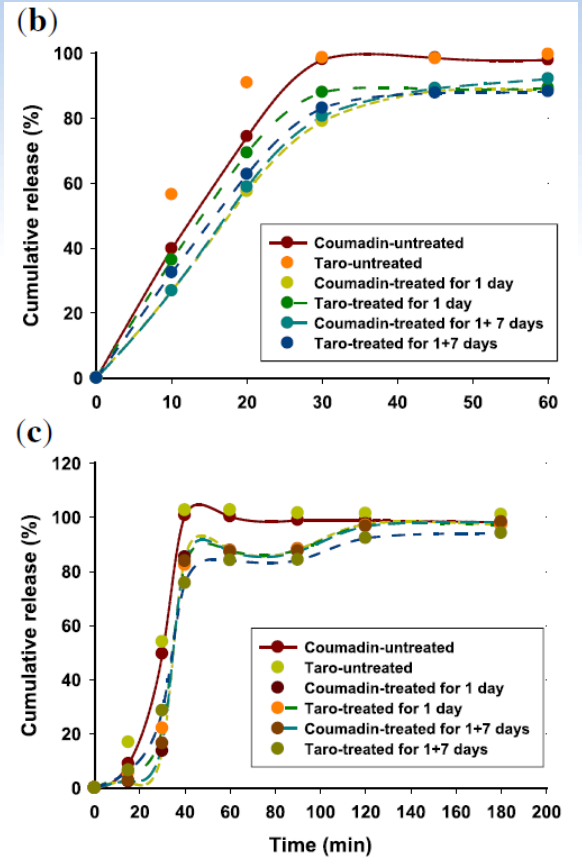
M&S and clinical study to assess the impact of product quality change on its in vivo performance

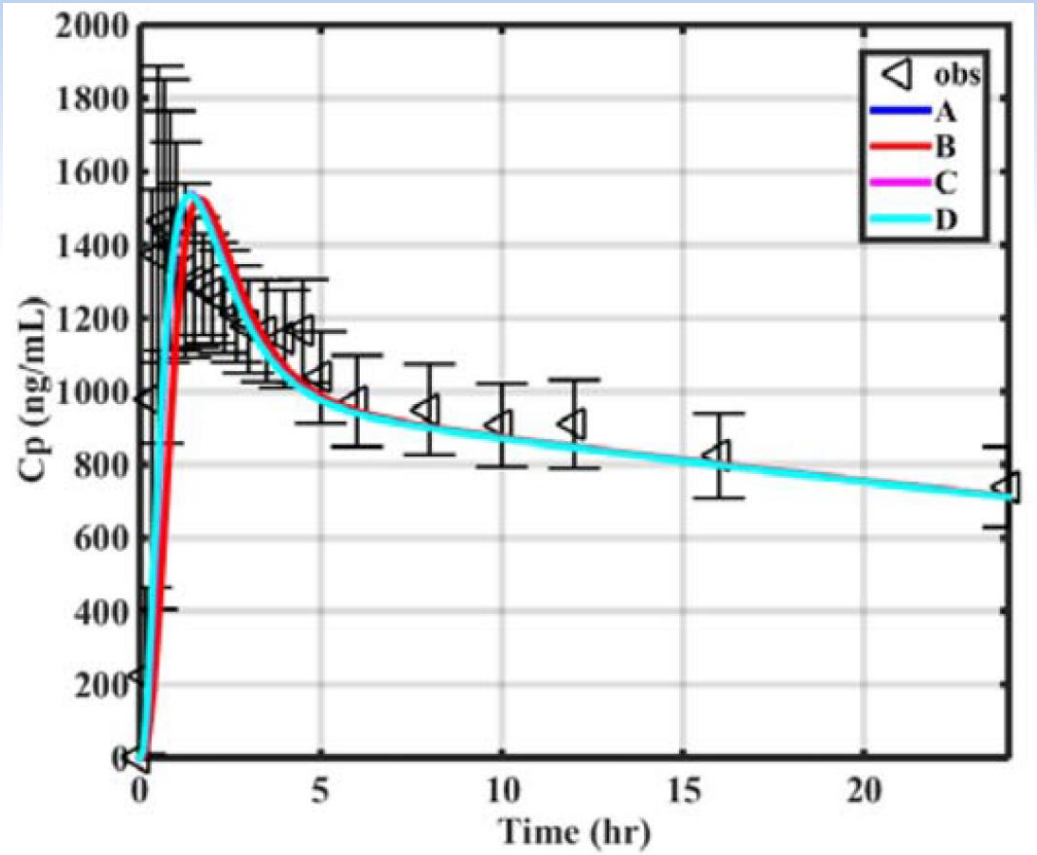
2 formulations (Coumadin & Taro) and 3 conditions:

- 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)

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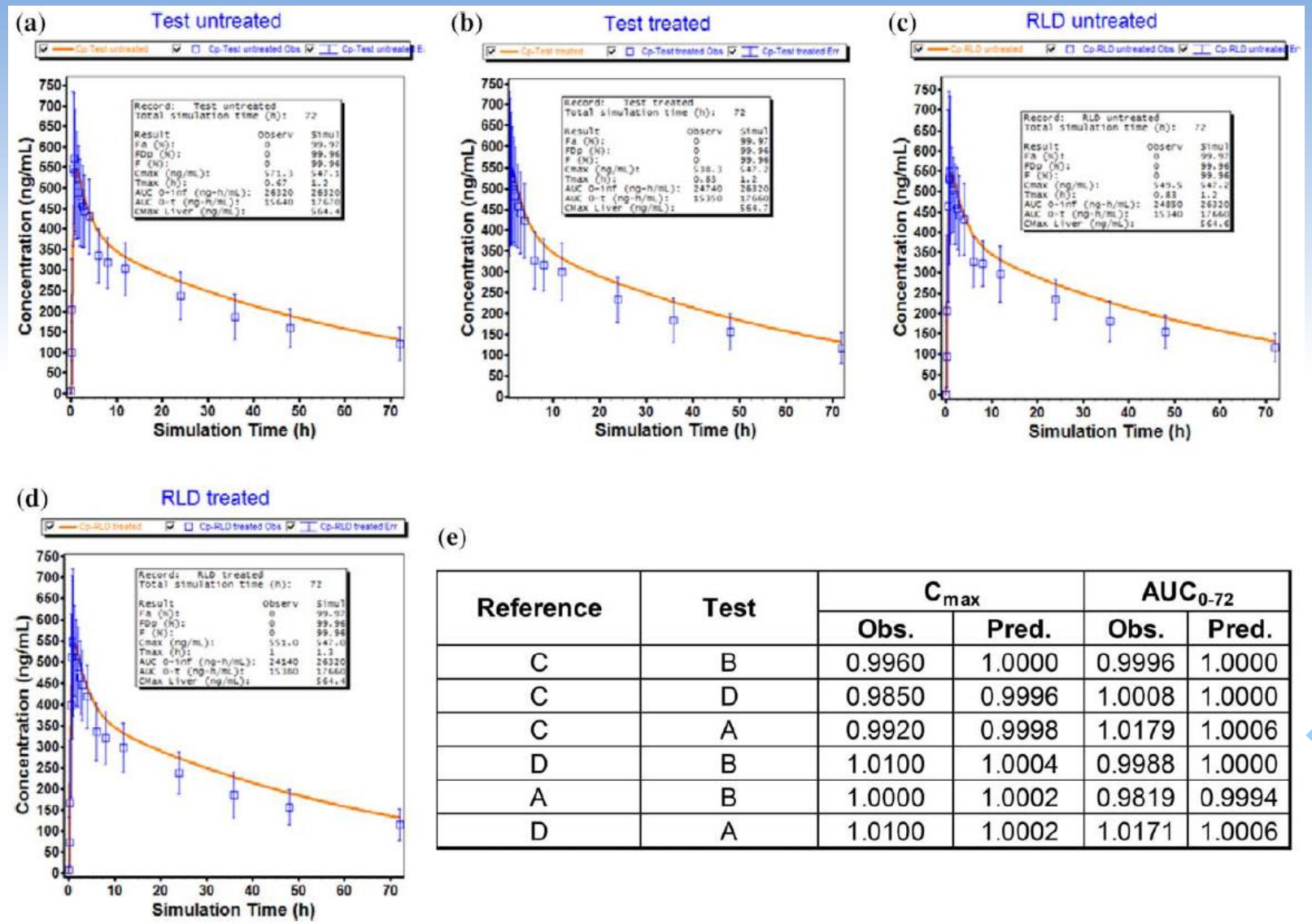
Virtual and Clinical Bioequivalence

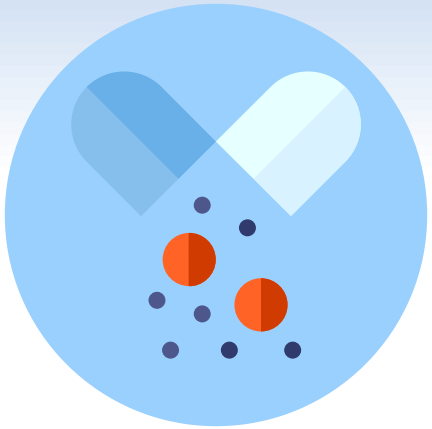


(e)

Reference	Test	C_{max}		AUC_{0-72}	
		Obs.	Pred.	Obs.	Pred.
C	B	0.9960	1.0000	0.9996	1.0000
C	D	0.9850	0.9996	1.0008	1.0000
C	A	0.9920	0.9998	1.0179	1.0006
D	B	1.0100	1.0004	0.9988	1.0000
A	B	1.0000	1.0002	0.9819	0.9994
D	A	1.0100	1.0002	1.0171	1.0006

PE between reference and test

In addition, PBPK modeling aids in defining in vivo relevant dissolution space

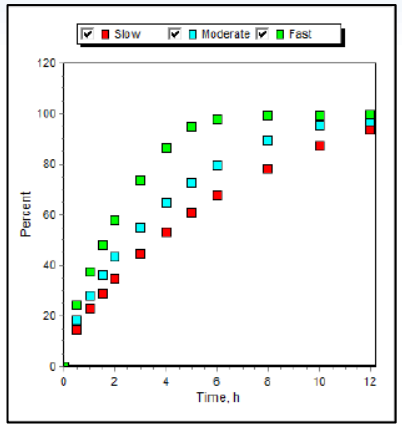


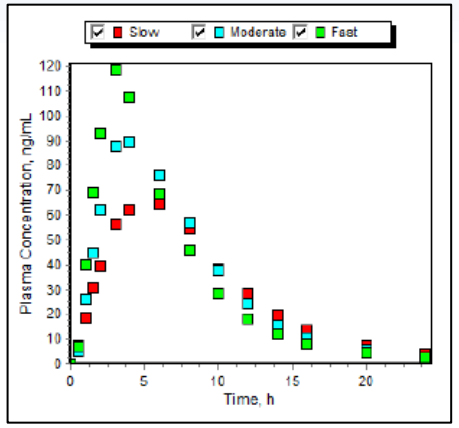
MR Formulation

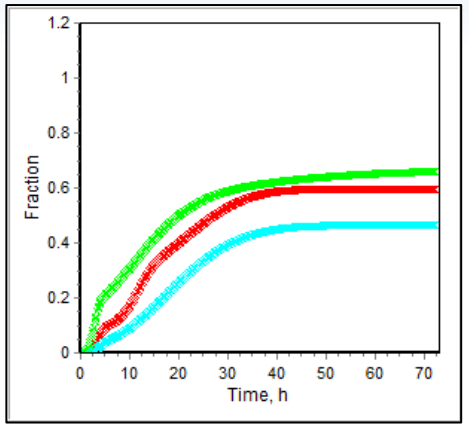
IVIVC

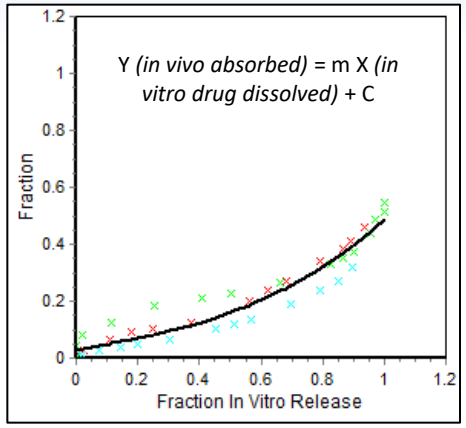
An IVIVC is a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response

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

The AAPS Journal (2019) 21:19
DOI: 10.1208/s12248-019-0292-3

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 Filippos Kesisoglou[7,8]

Case Study

IVIVC for MR formulation for a BCS III candidate drug development

Kesisoglou, AAPS J. 2015

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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:

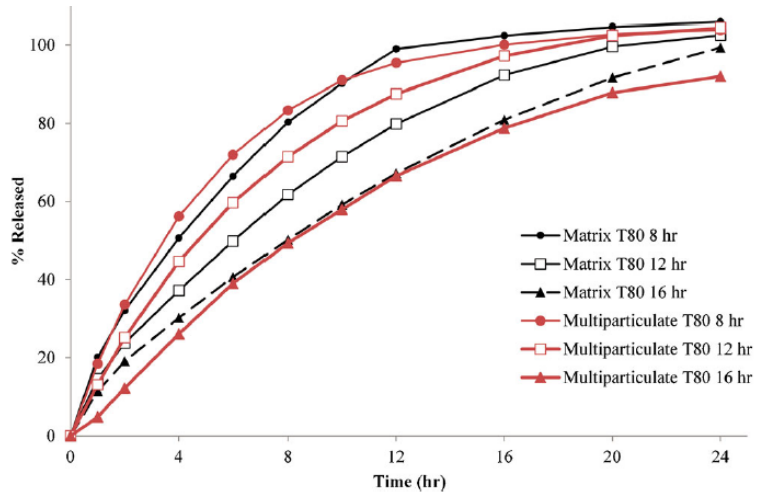


Fig. 1. Average (n=6) dissolution profiles for matrix and multiparticulate MK-0941 formulations used for IVIVC model development

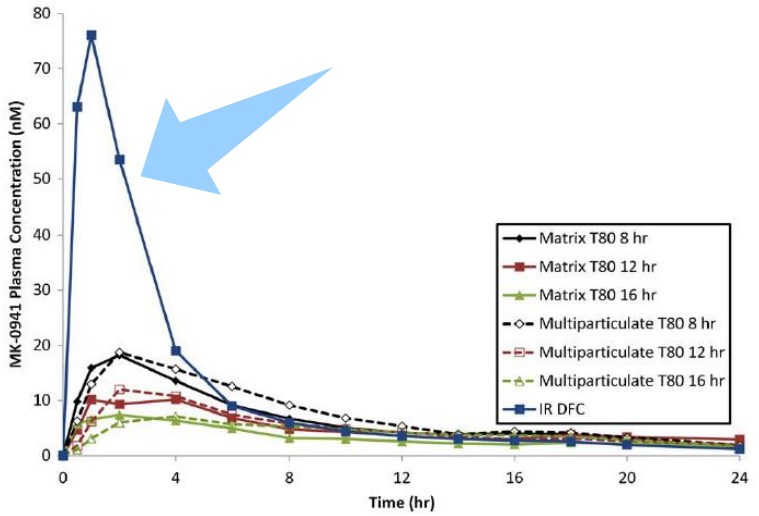


Fig. 2. Mean (n=16) plasma concentration *vs.* time profiles for MK-0941 IR and ER formulations

Mechanistic IVIVC

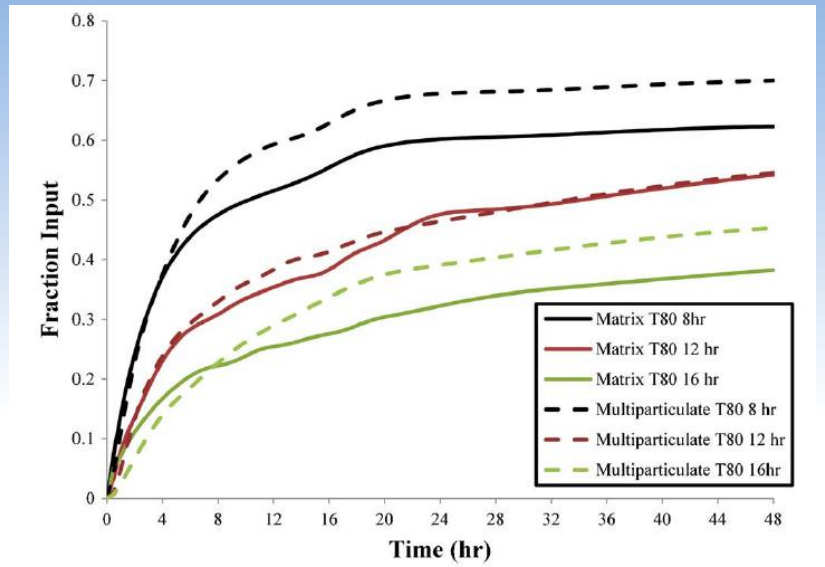


Fig. 3. Average fraction input *vs.* time profiles for MK-0941 ER formulations estimated by deconvolution

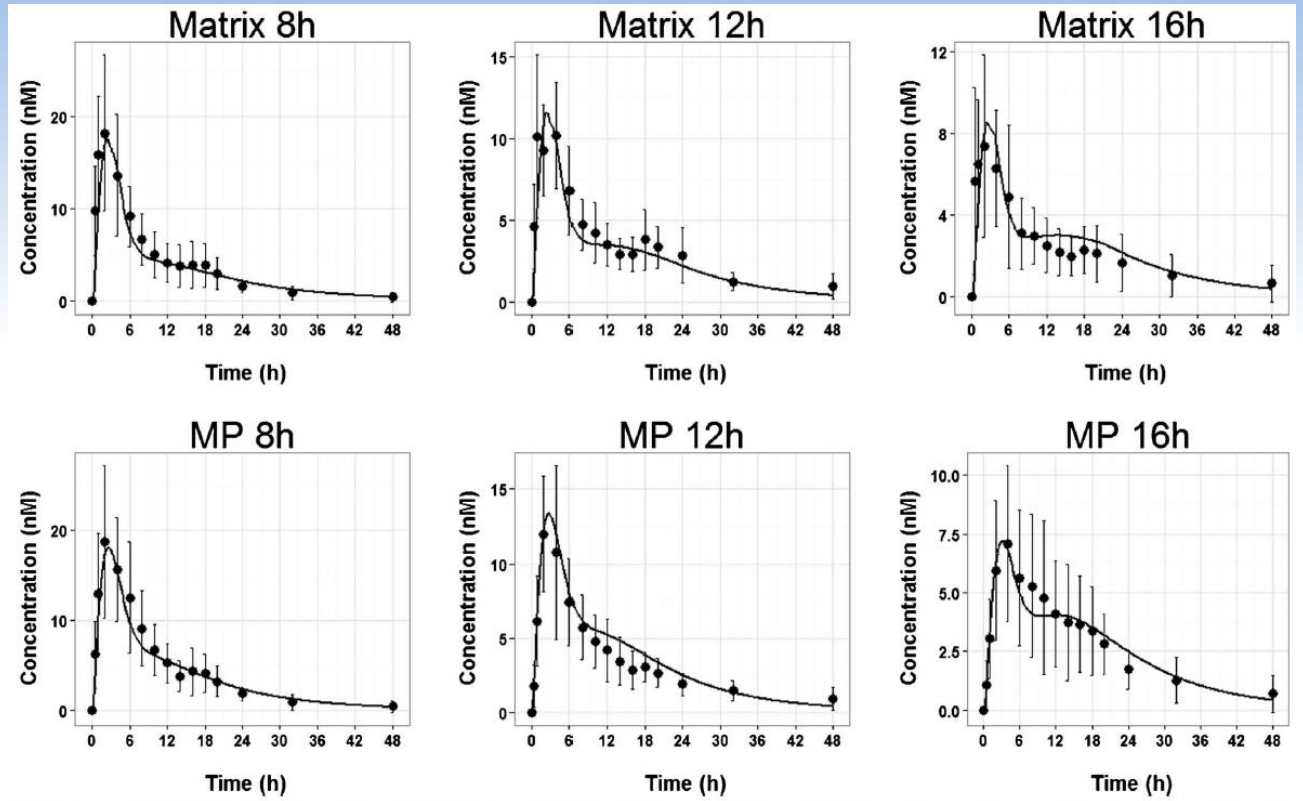
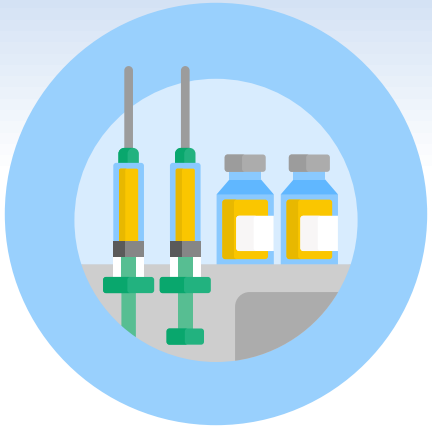


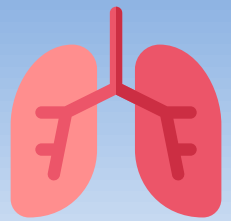
Fig. 6. Absorption PBPK IVIVC model predicted (*lines*) *vs.* observed (*squares*, mean ± SD) plasma concentration *vs.* time profiles for MK-0941 ER formulation

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



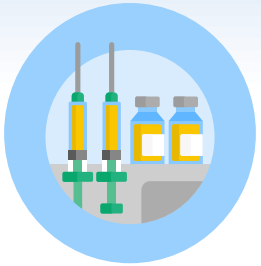
Other routes of administration

Pulmonary

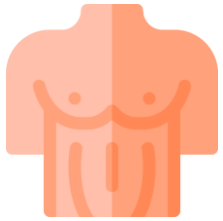


Ocular

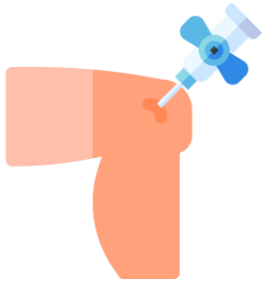
Intra-muscular



Dermal



Intra-articular



Oral Cavity

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!

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