





PBPK Modelling and Simulation: An In Silico - In Vivo Bridge for Efficient Formulation Development

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Disclaimer:

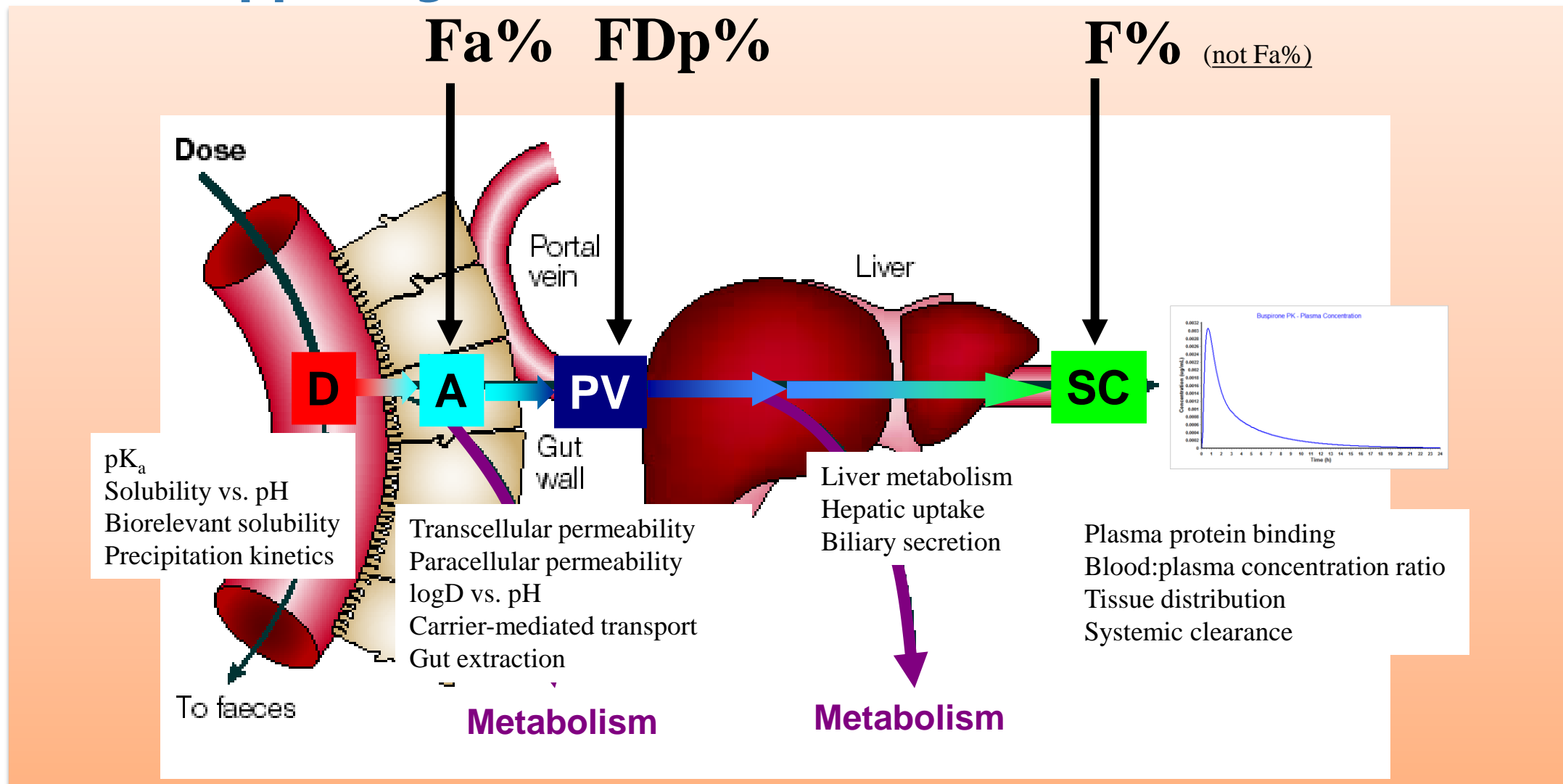
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Introduction to PBPK Modelling and Simulation

PBPK M&S ?

- Physiologically **B**ased **P**harmacokinetic **M**odelling & **S**imulation
- A mathematical modelling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species
 - Wikipedia
- A PBPK model is defined as one that simulates the concentration of a drug over time in tissue(s) and blood, by taking into account the rate of its absorption into the body, distribution in tissues, metabolism and excretion (ADME) on the basis of interplay among critical physiological, physicochemical and biochemical determinants.
 - EMEA guideline (EMA/CHMP/458101/2016)

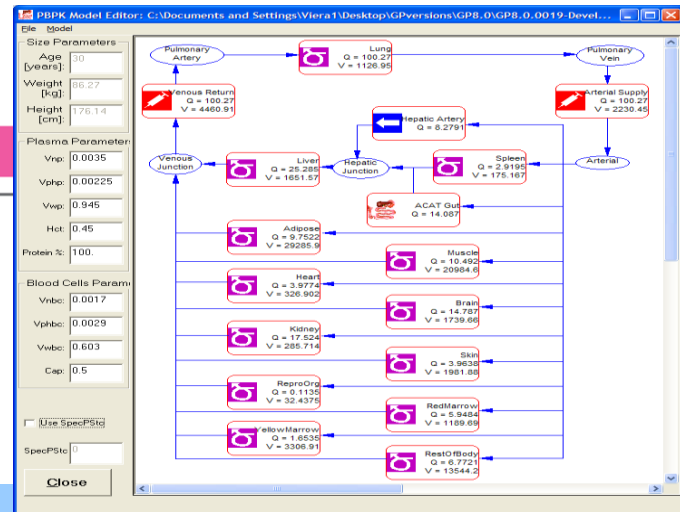
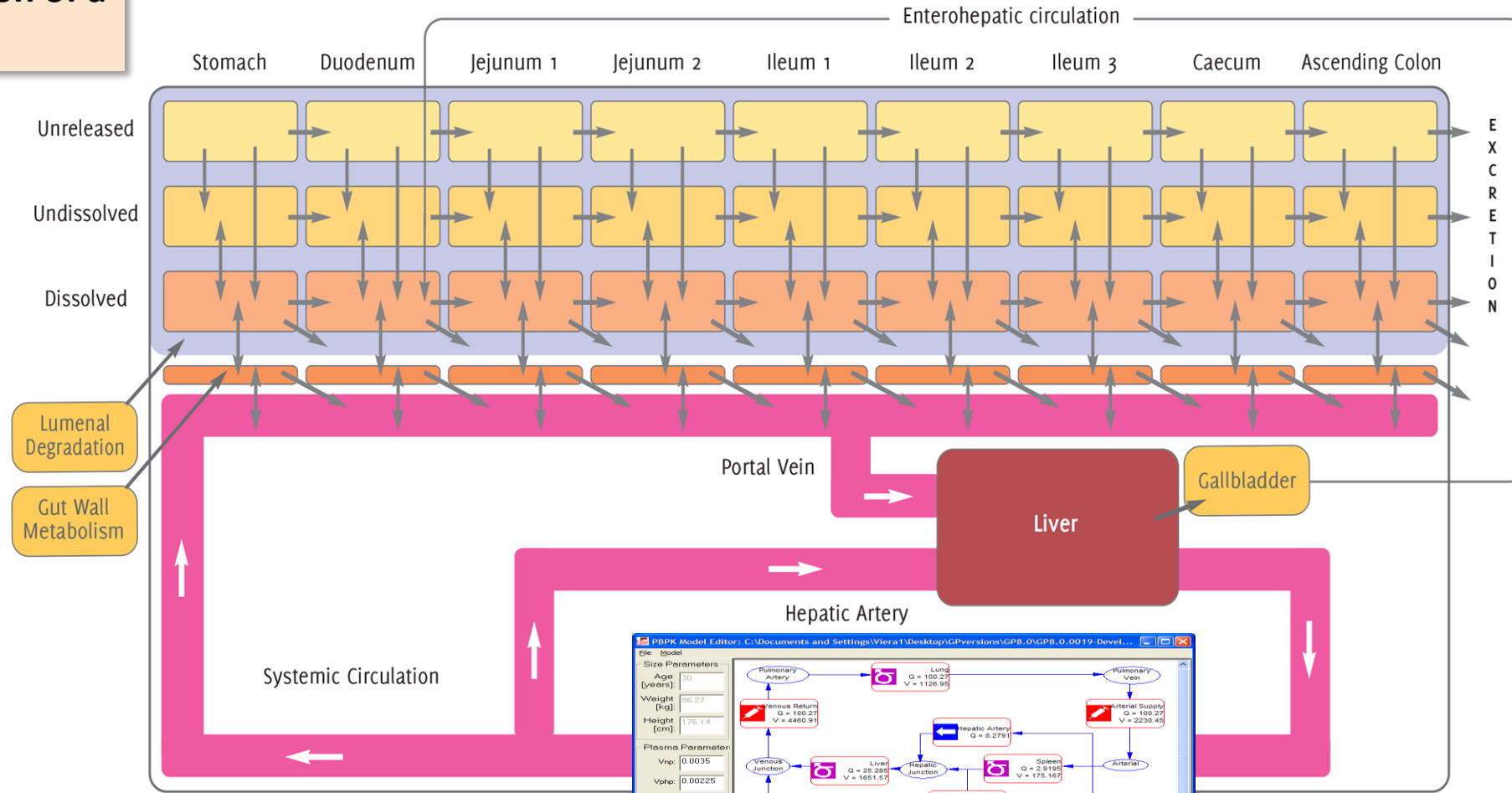
What's happening in vivo? (after oral administration)



* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

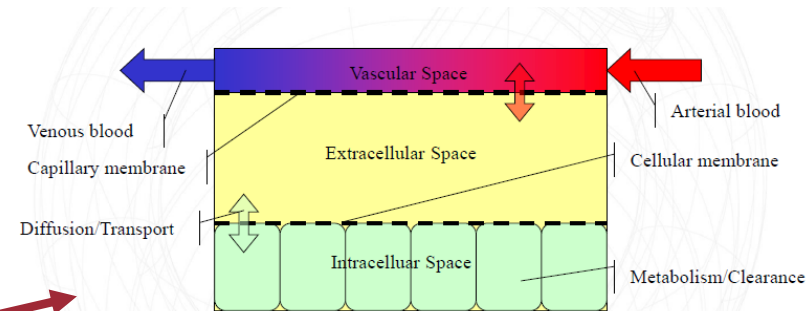
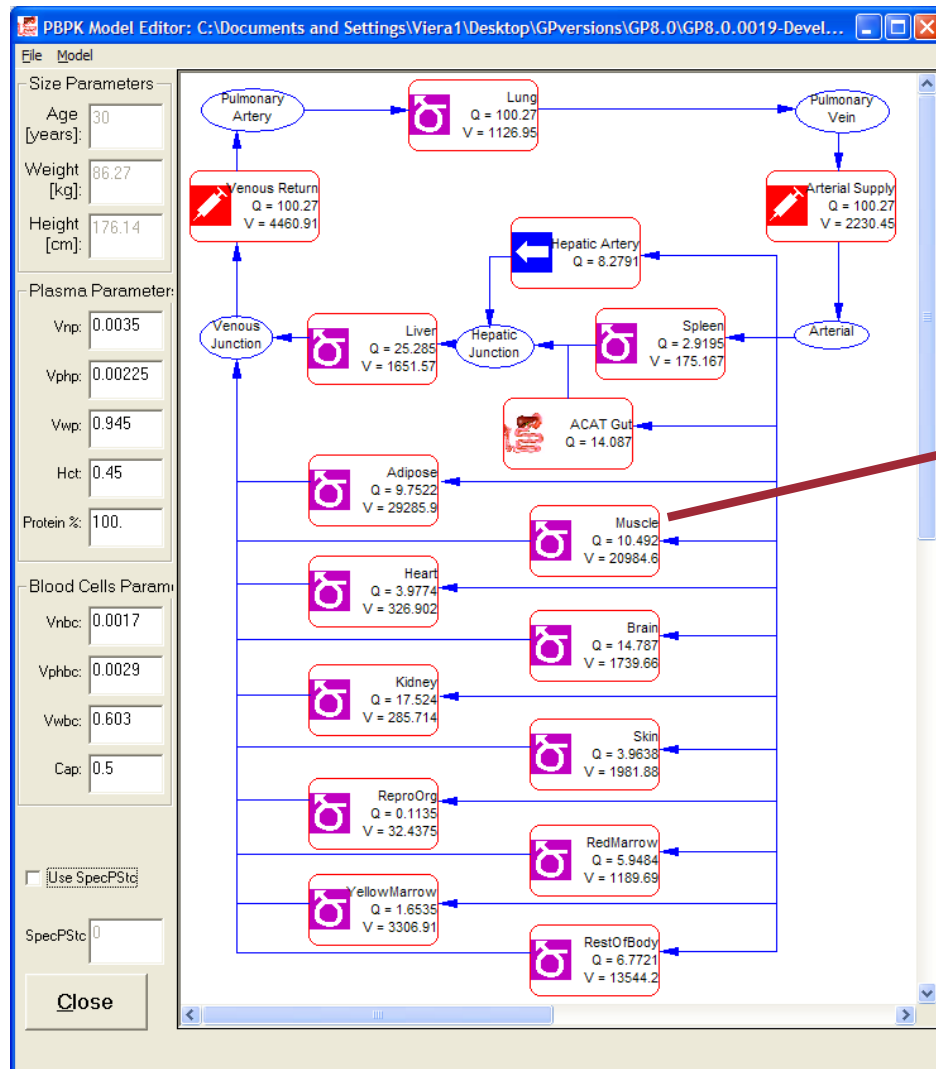
Schematic representation of a PBPK model

Advanced Compartmental Absorption and Transit Model (ACAT™)



Slide courtesy of Simulations Plus Inc.

What's defined in a PBPK model?



$$V_t \frac{dC_t}{dt} = \left(Q \times C_{bi} - \frac{Q \times C_t \times R_{bp}}{K_p} - CL_{int,u} \left(\frac{C_t \times f_{u,p}}{K_p} \right) \right)$$

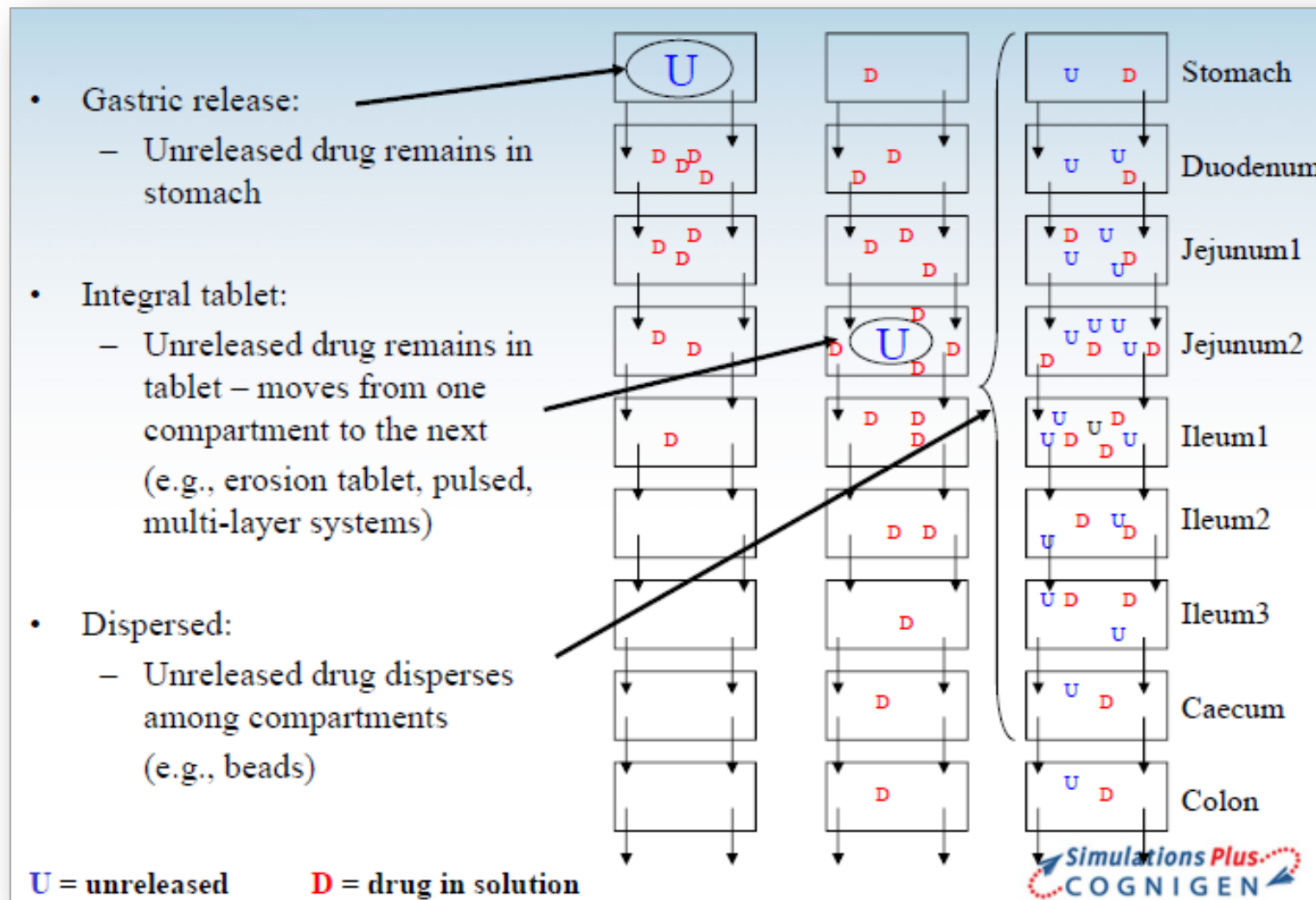
- Each compartment represents a tissue:
 - Specific volume(s)
 - Blood perfusion rate
 - Enzyme/transporter expression levels
 - Volume fractions of lipids & proteins
 - Tissue:plasma partition coefficient (K_p)

Slide courtesy of Simulations Plus Inc.

Key components of a PBPK Model

- Model structure
 - Each compartment is defined by a tissue volume (or weight) and tissue blood flow rate
 - Perfusion rate limited: e.g. small lipophilic molecules, where the blood flow to tissue becomes the limiting process
 - Permeability rate limited: e.g. larger polar molecules, where the permeability across the cell membrane becomes the limiting process
- System-related inputs
 - Mouse, rat, dog, human etc.
 - Hepatic blood flow, CYP, liver volume etc.
 - Diseased states, pregnancy, obesity, elderly, paediatrics etc.
 - Include sources of physiological and biochemical variability
- Drug-specific inputs

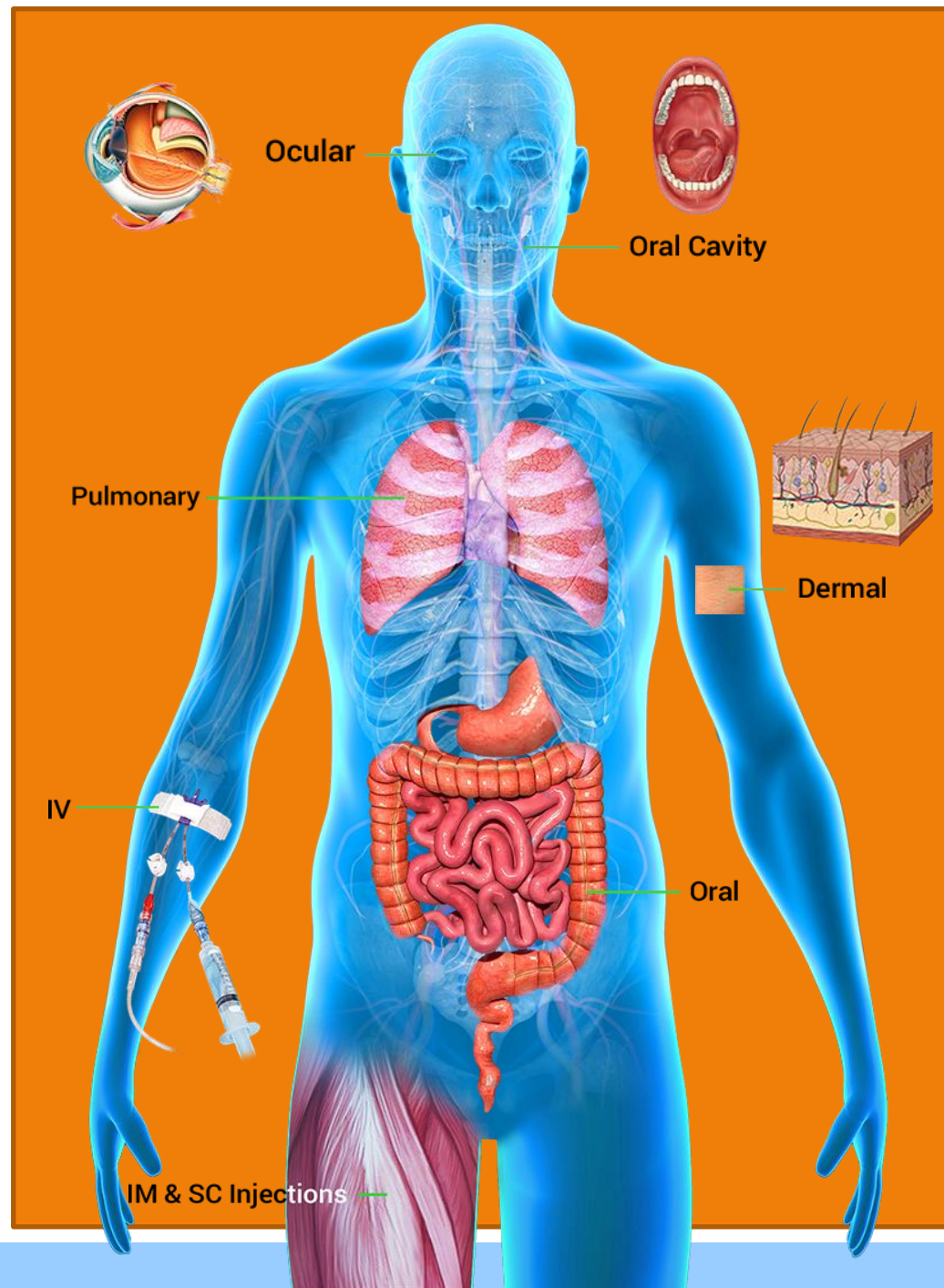
Dosage forms in a mechanistic way within ACAT™ model



Slide courtesy of Simulations Plus Inc.

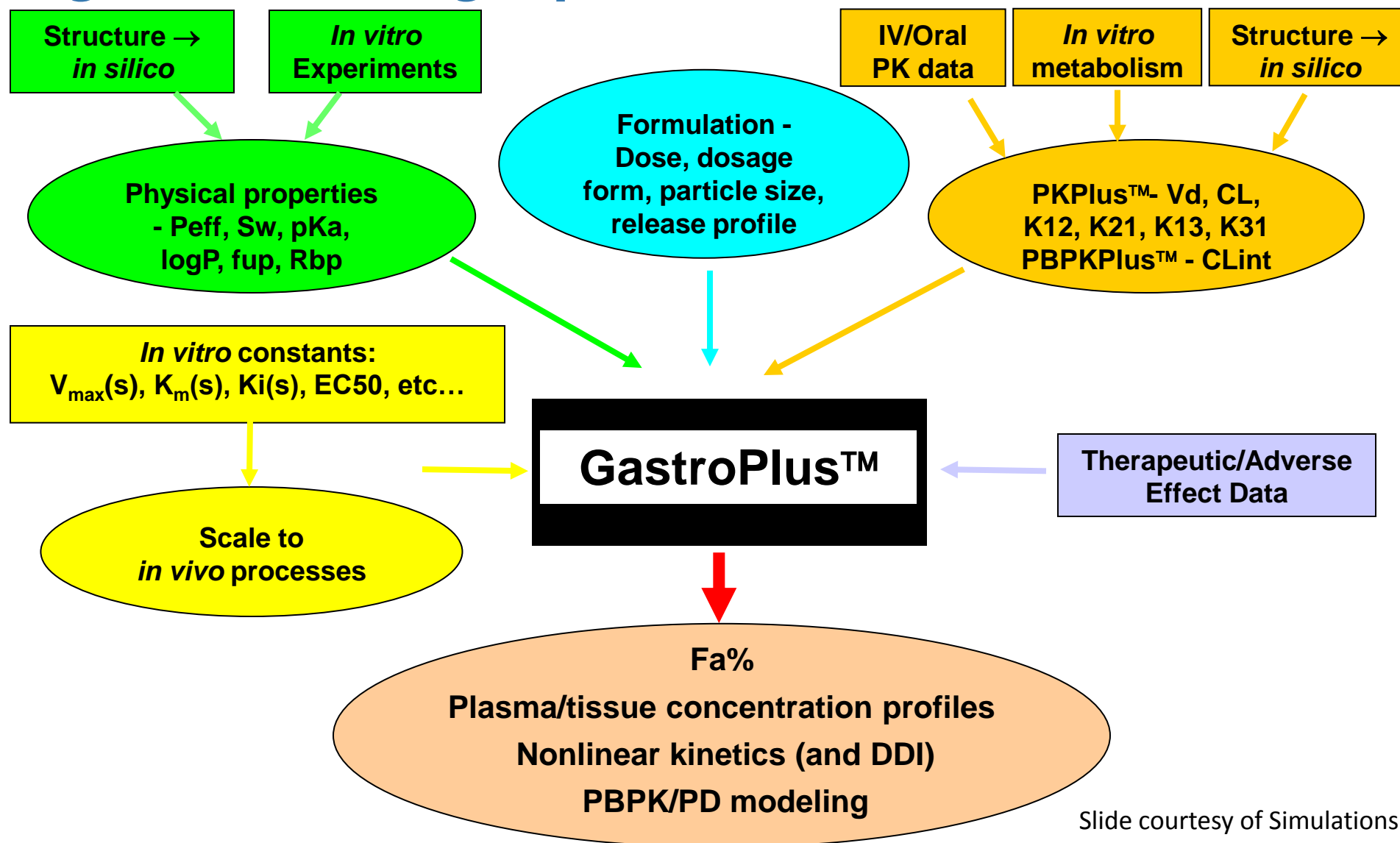
Other routes

- Mechanistic absorption models (MAM) coupled with compartmental/PBPK modelling have been extended to cover all major routes of administration



Slide courtesy of Simulations Plus Inc.

The Big Picture – Drug Inputs



Slide courtesy of Simulations Plus Inc.

IVIVR/IVIVC: Traditional Vs PBPK approach

Common approaches for IVIVR/IVIVC

- IVIVR / IVIVC / IVIVE
 - A mathematical link
- Deconvolution
 - Plasma concentration profile to in-vivo fraction
- Convolution
 - In-vivo fraction to plasma concentration profile
- Traditional Methods
 - Compartmental (Wagner-Nelson, Loo-Riegelman)
 - Numerical

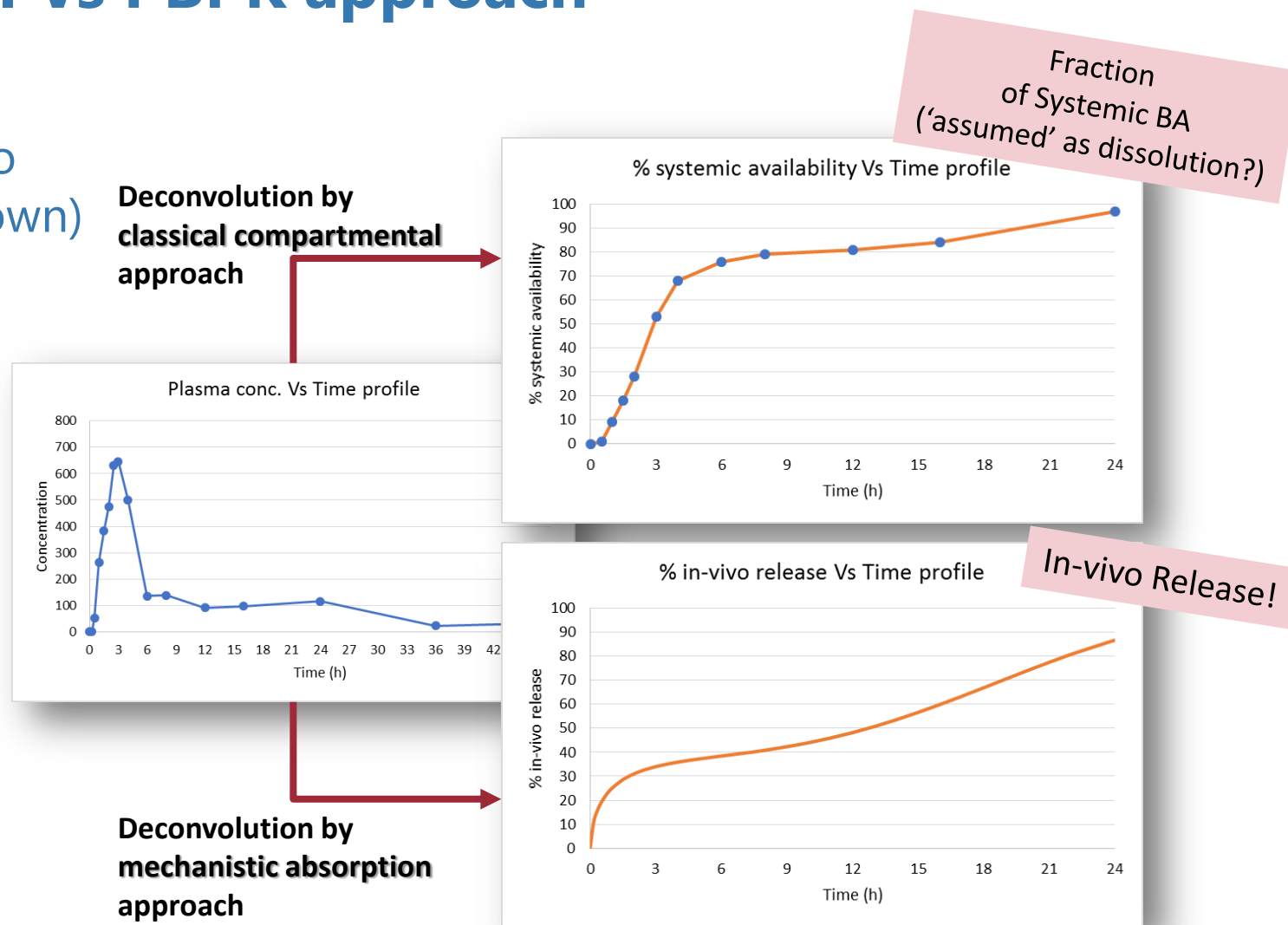
Classical compartmental Vs PBPK approach

- Plasma concentration to in-vivo fraction of systemic BA (top-down)

- Compartmental, Numerical
- K_a constant across GIT
- Simpler approach

- In-silico plus in-vitro to In-vivo dissolution and plasma/ tissue concentrations (bottom-up)

- Mechanistic: ACAT, PBPK
- Detailed, scientific approach
- Ability to 'simulate' / 'extrapolate' (IVIVE)



Mechanistic absorption based PBPK approach

- Inputs (in addition to the data required for the traditional methods):
 - Physiological parameters
 - Drug properties (solubility, P_{eff} , $\log P$, pK_a , etc.)
- Outputs:
 - A model that combines all available in-silico, in-vitro and in-vivo information and provides:
 - In vivo dissolution, absorption and bioavailability vs. time profiles
 - Description of site dependent absorption
 - Description of tissue contributions to first pass extraction

IVIVR/IVIVC Case Studies

Case Study 1: Effect of PK modelling approach

- NDA- Modified generic product [502(b)2]
- IR Tablets of 'Compound A'
- BCS Class: I
- API: Water soluble salt
- pKa: 8.0 to 8.5
- cLogP: 2.0 to 2.5
- Permeability (P_{eff}, ADMET Predictor 8.1): $\sim 4.0 \times 10^{-4}$ cm/s
- Product design: Modify the release profile to marginally meet the bio-equivalence with a C_{max} %T/R ratio of close to $\sim 85\%$.
- PBPK Modelling platform: GastroPlus™ 9.5

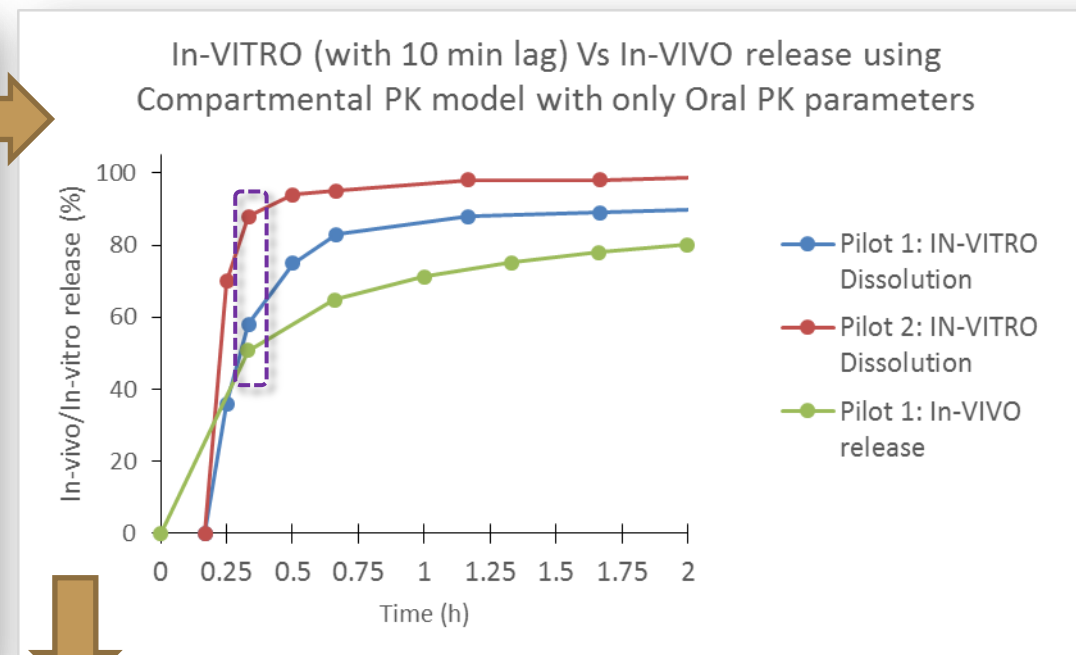
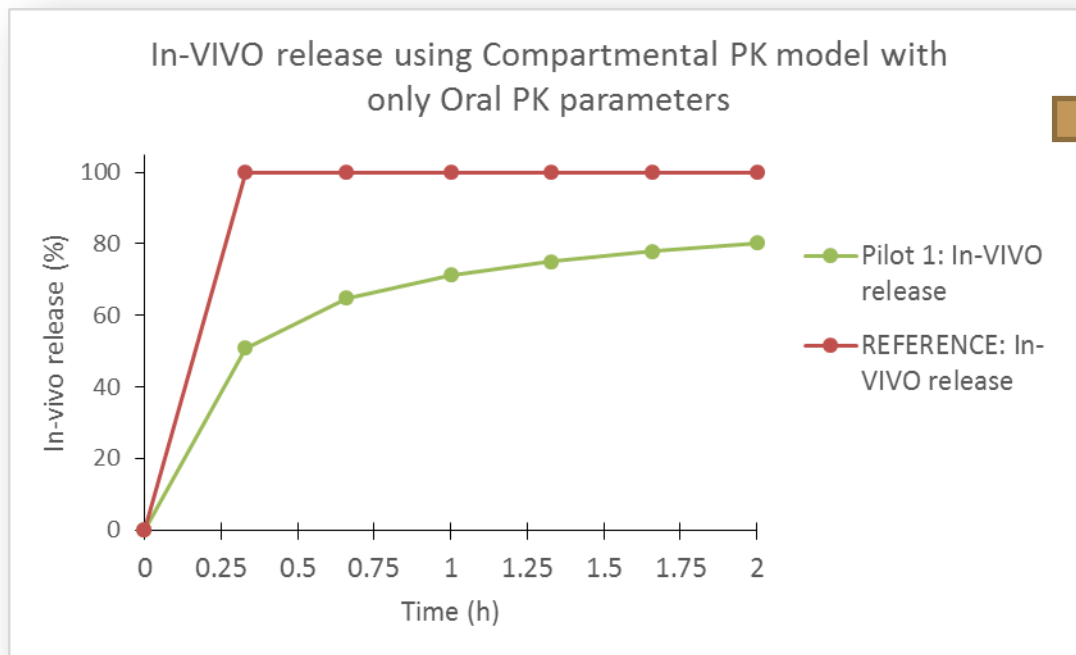
Case Study 1: Effect of PK modelling approach (contd.)

- Results of 1st pilot PK study

PK Parameter	Pilot #1
C_{\max}	67%
AUC_{0-t}	102%

- Initial model was developed using ACAT coupled with Compartmental PK model based on only Oral human PK data (Solution and Tablet).
- V_d and Cl estimated by I.V. route, as well as absolute oral BA estimates were not available in literature.

Case Study 1: Effect of PK modelling approach (contd.)



Batch	In-vitro dissolution at 10 min (%)	In-vivo release at 20 min (%)	In-vivo release at 40 min (%)
Pilot 1	58	51	65
Pilot 2	88	77 (predicted)	98 (predicted)

Case Study 1: Effect of PK modelling approach (contd.)

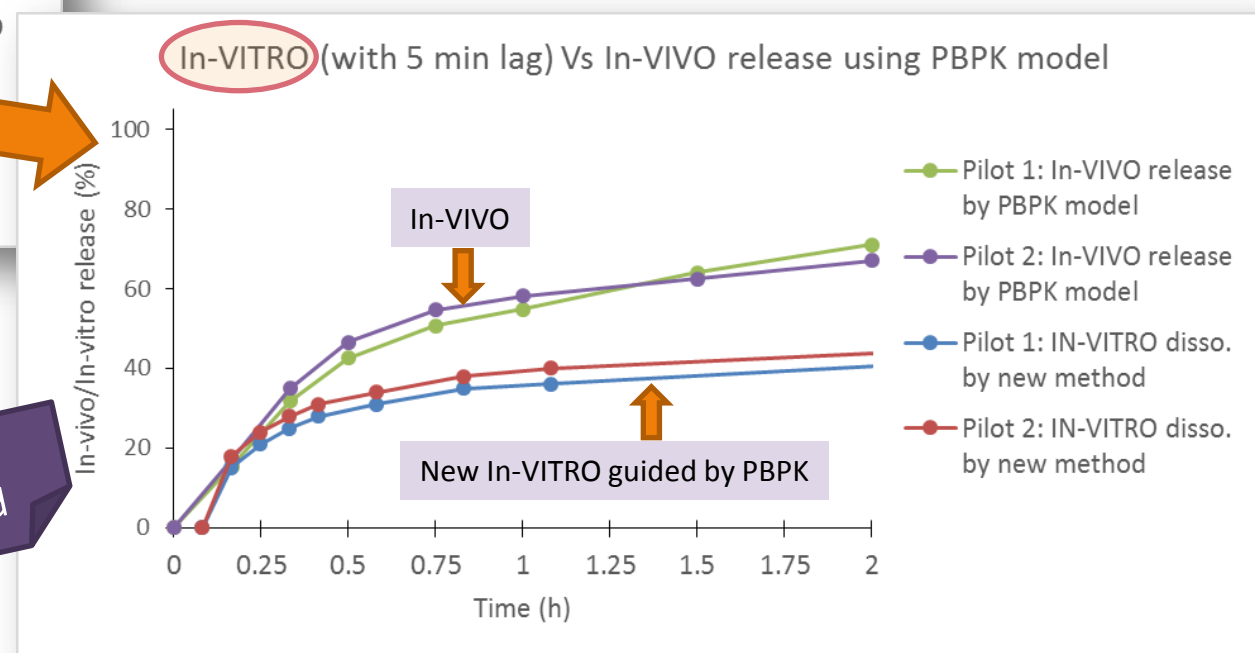
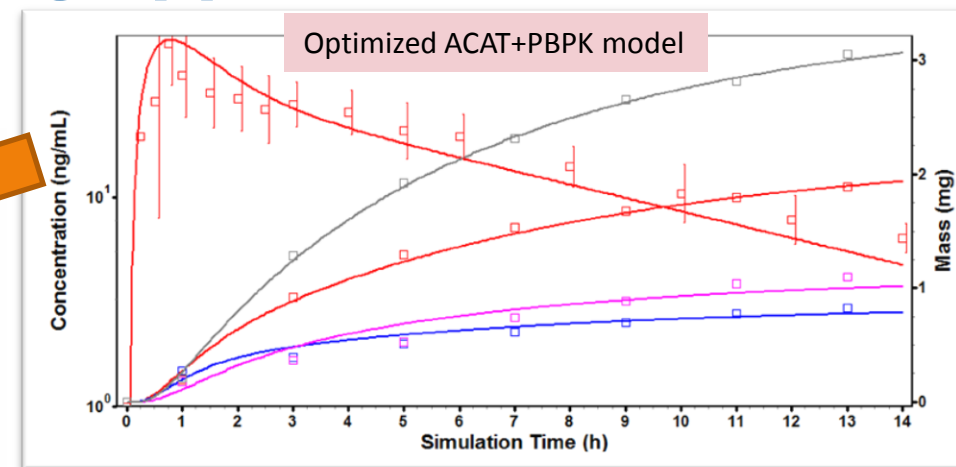
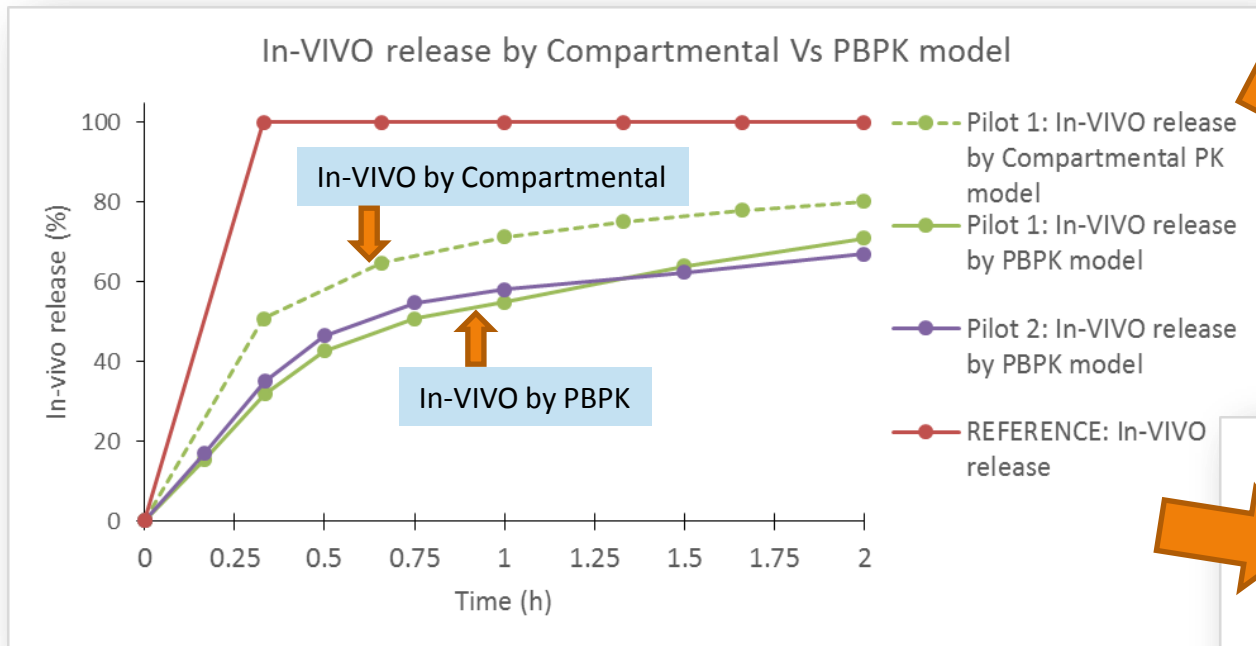
- Results of 2nd pilot PK study

PK Parameter	Pilot #1	Pilot #2
C_{\max}	67%	70%
AUC_{0-t}	102%	99%

only ~3% rise in the ratio!!!

- Dissolution method was guided by PK model
 - Absence of true estimates of V_d and systemic Clearance
- Model re-developed by ACAT coupled with PBPK model, which was optimized using plasma and urine analysis data of active and metabolites
 - V_d was estimated to be 194 L, compared to ~320 - 400 L
 - Oral BA was estimated to be ~55%

Case Study 1: Effect of PK modelling approach (contd.)



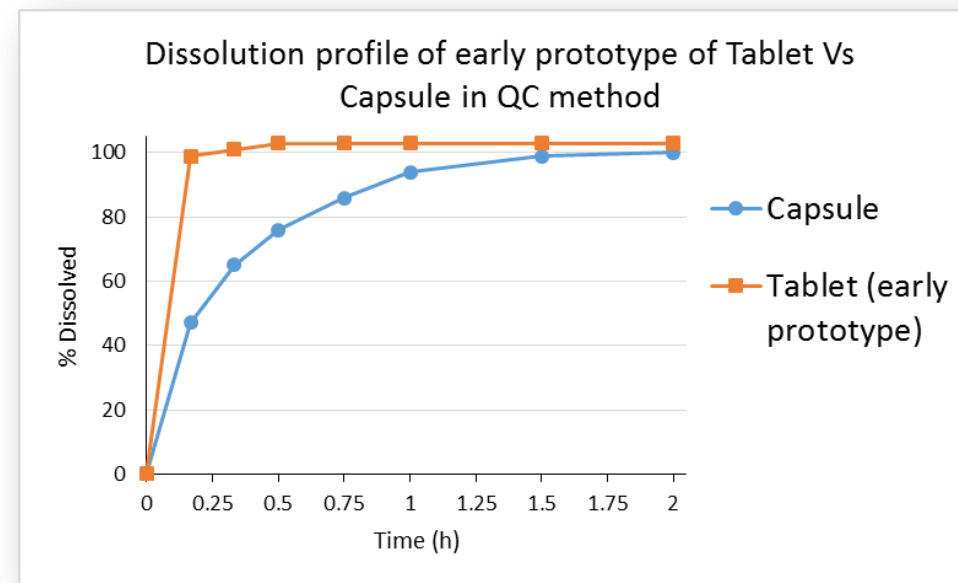
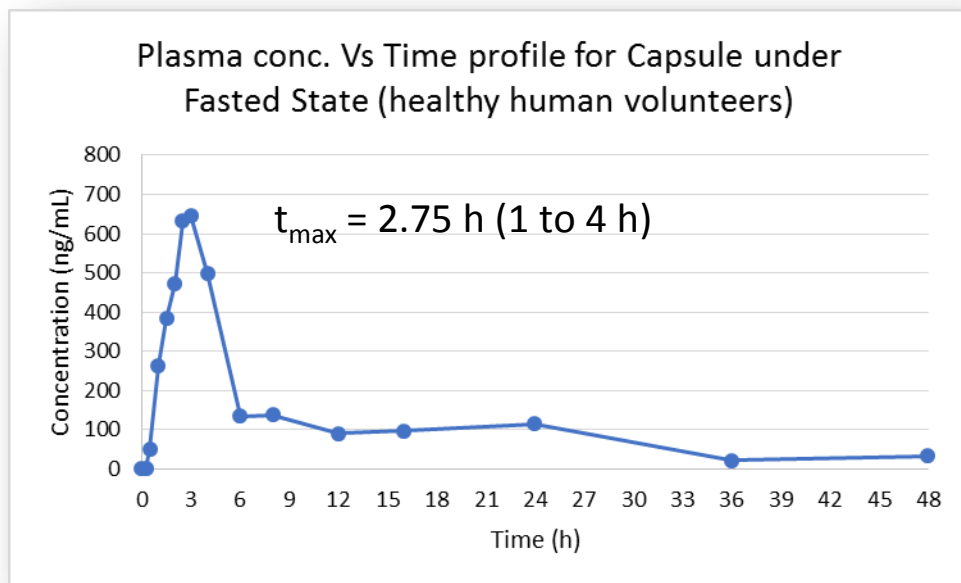
Better confidence in new in-VITRO method

Case Study 2: Formulation switch for a NCE

- NDA- NCE
- IR Capsules of 'Compound B'
- BCS Class: II
- API: Practically insoluble in water
- pKa: Base = 2.5 to 3.0, Acid = 9.0 to 9.5
- Log D: 3.0 to 3.5 @ pH 7.45
- Permeability (Caco-2): 3.5×10^{-6} cm/sec
- Product design: Enabling formulation for improved solubility and oral bioavailability.
- Study objective: Identify a bio-relevant dissolution condition for screening formulations for formulation switch.
- PBPK Modelling platform: GastroPlus™ 9.5

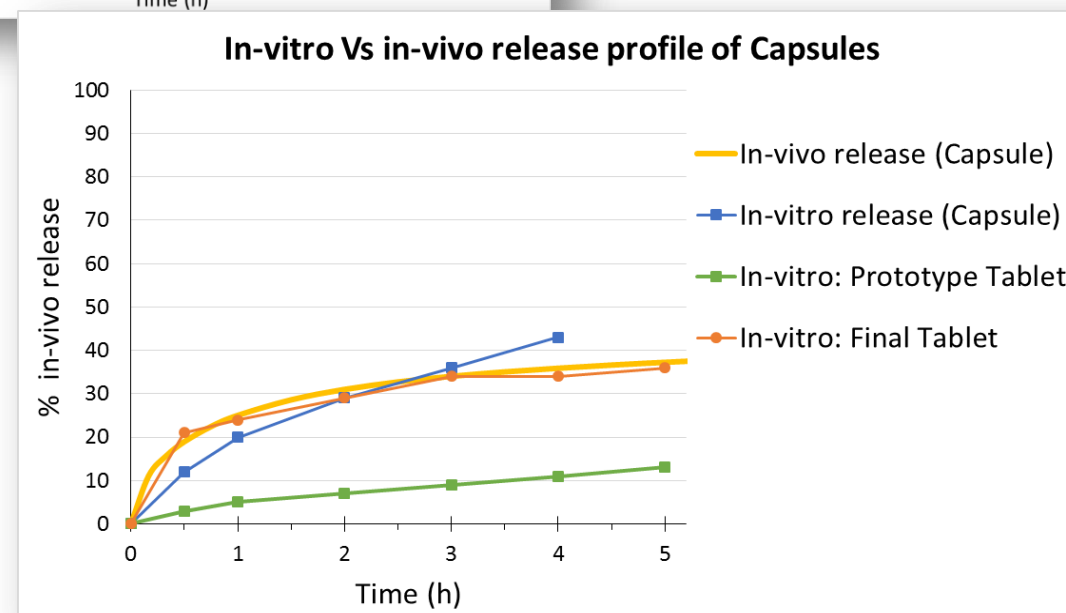
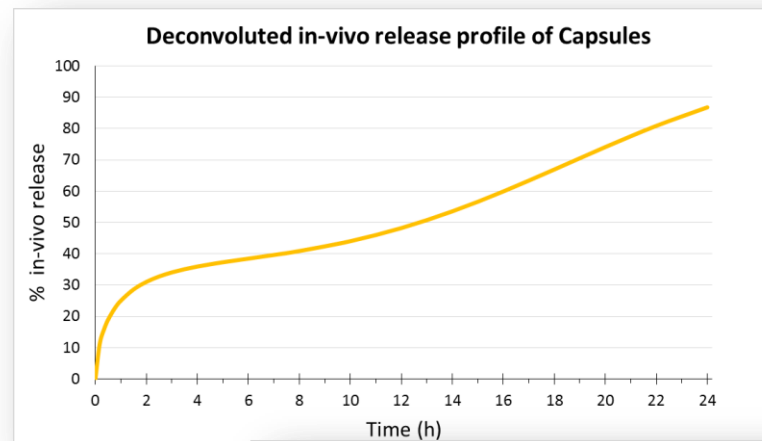
Case 2: Formulation switch for a NCE (contd.)

- Does the capsule release complete drug in-vivo?
- Is there any possibility of in-vivo precipitation?
- Is the QC method under/over discriminatory?



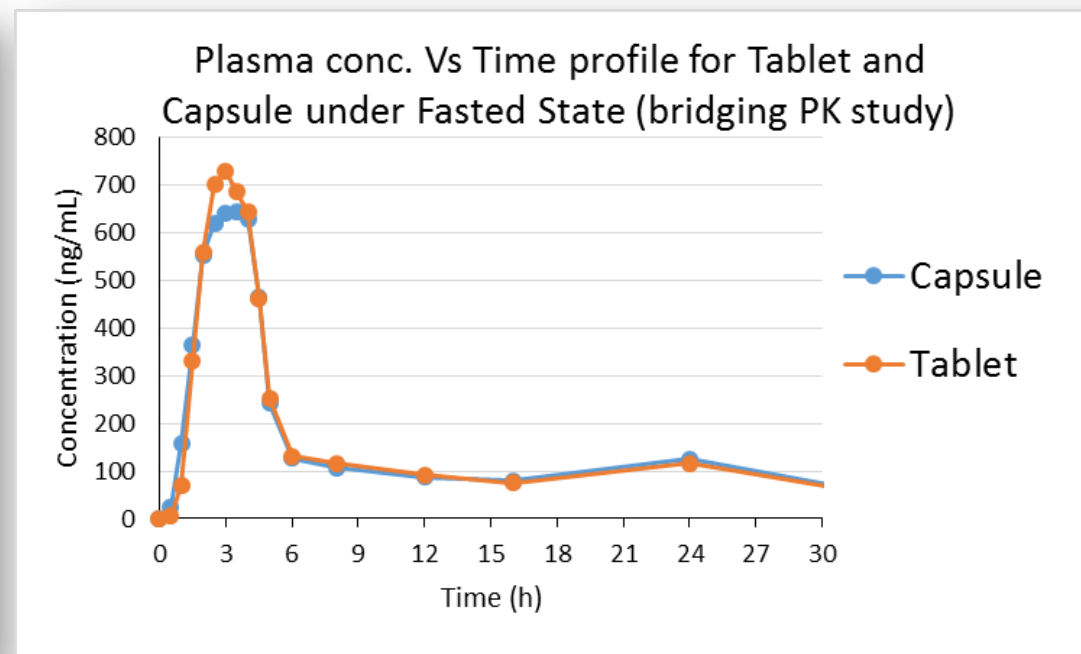
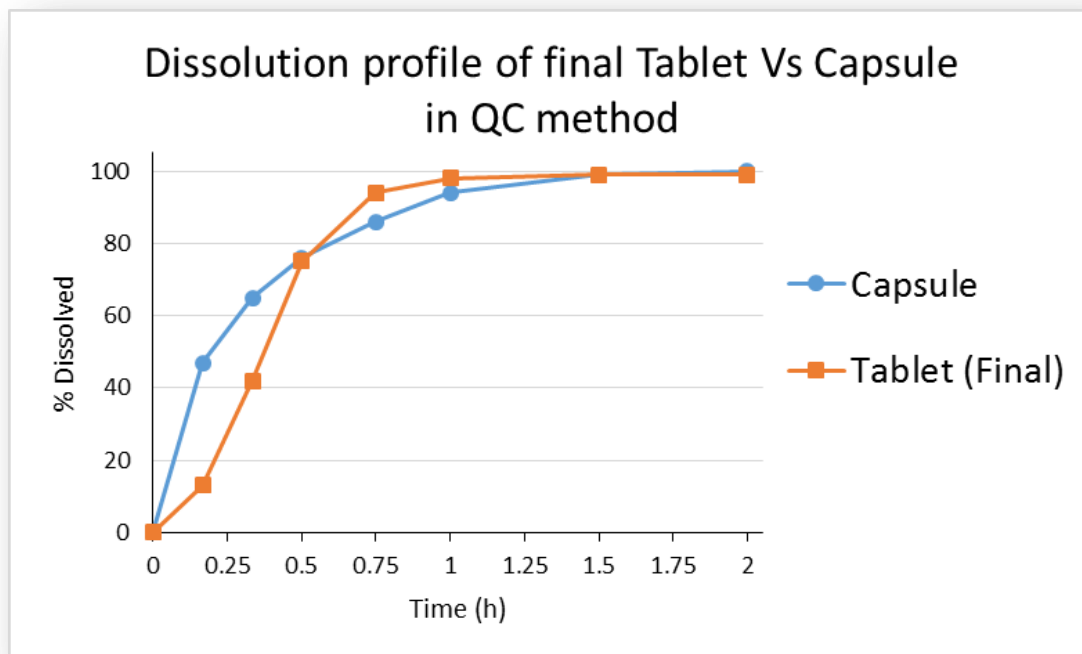
Case 2: Formulation switch for a NCE (contd.)

- Mechanistic deconvolution based on ACAT coupled with PBPK modelling
- In-vivo precipitation followed by slow and sustained dissolution
- C_{max} is resulting from dissolution of only 20-40% of drug
- Bio-relevant dissolution method
 - Non-sink conditions
 - Optimization of tablet formulation for bridging study



Case 2: Formulation switch for a NCE (contd.)

- Bridging PK study
 - Tablet was bio-equivalent to capsule



Regulatory acceptance

PBPK@US-FDA and EMEA

Well acknowledged and promoted by regulatory agencies, like US-FDA and EMEA



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft

...the format and content of PBPK analyses that are submitted to the FDA vary significantly across drug developers



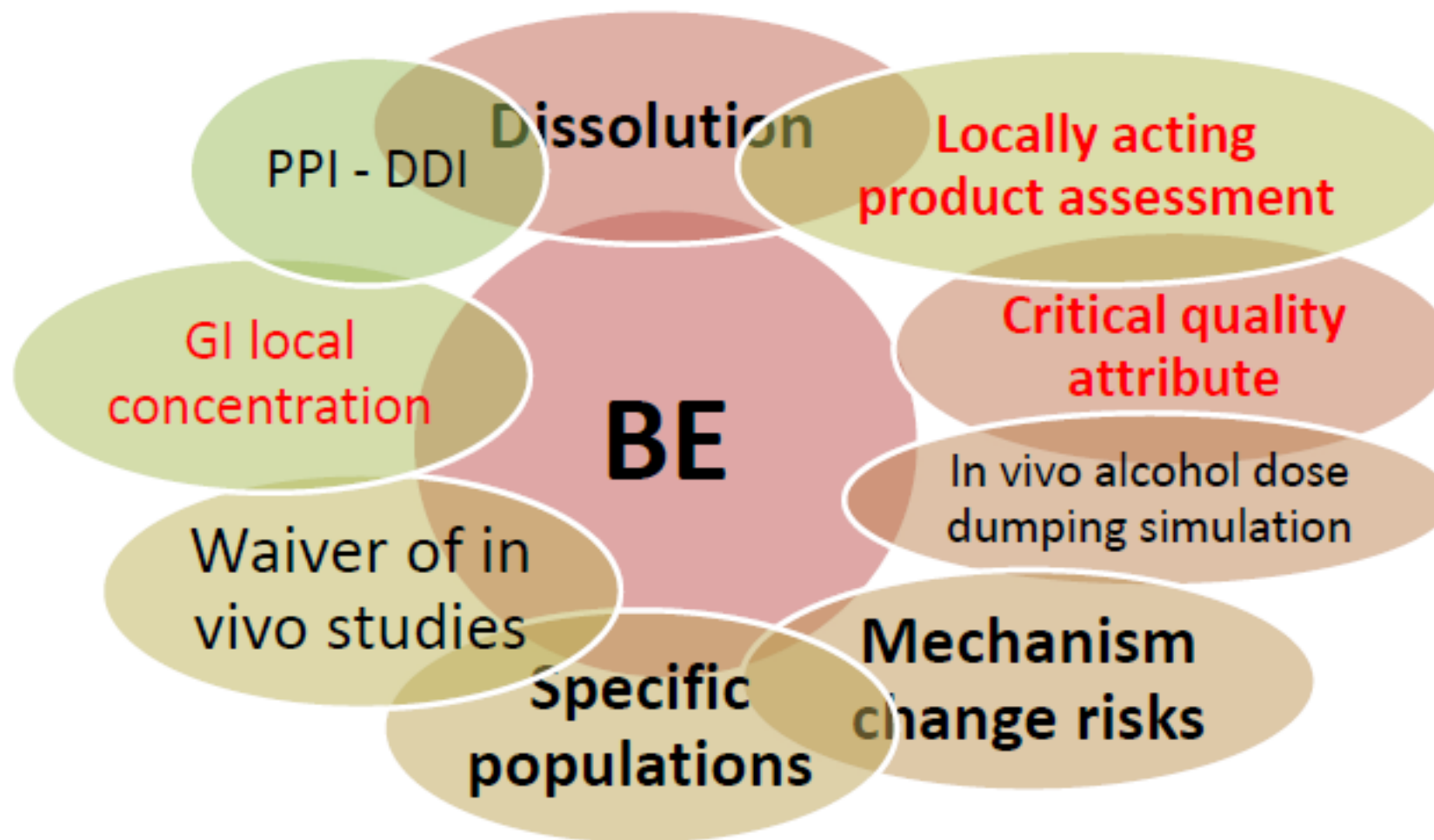
Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

DRAFT GUIDANCE
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2016
Clinical Pharmacology

...can facilitate FDA's efficient assessment, consistent application, and timely decision making during regulatory review

General PBPK Model Applications for Generic Products in the OGD, CDER, US-FDA



BE: bioequivalence;
 PPI : proton pump inhibitor; GI: gastrointestinal ; DDI: drug-drug interaction

Slide courtesy of L. Zhao, E. Tsakalozou (OGD, CDER, FDA; 2017)

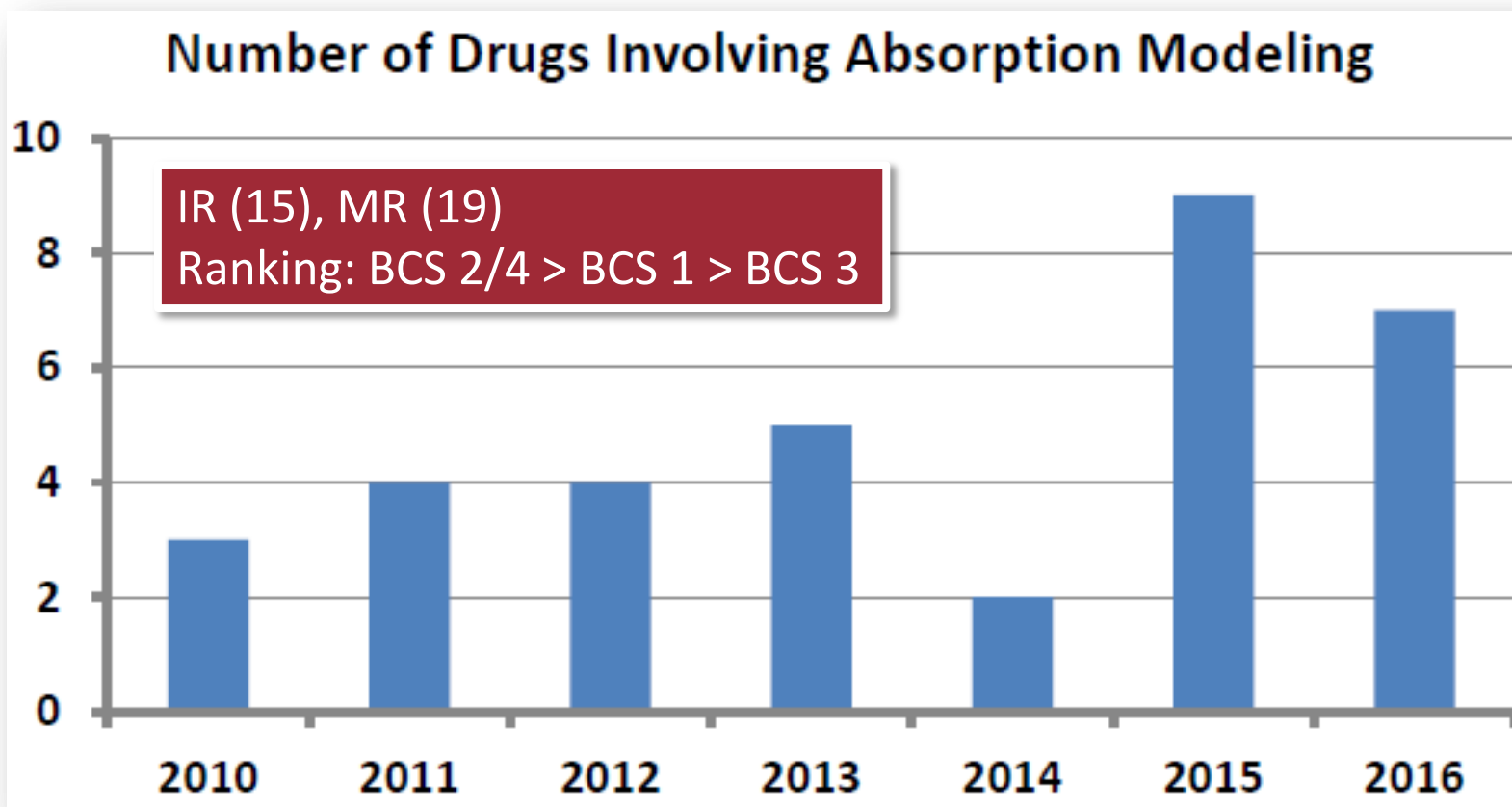
Highlights of PBPK M&S Impacts (Year 2016) in the OGD, *sparc* CDER, US-FDA

- Ibrutinib: PBPK Supported Detailed Actions for CYP3A Inhibitors in Drug Label
 - "...strong CYP3A inhibitors which would be taken chronically...is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed...Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used...Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity."

Co-medication	CYP3A modulation	Obs/Sim	AUC ratio	Cmax ratio
Ketoconazole	Strong inhibitor	Observed	27	31
Erythromycin	Moderate inhibitor	<u>SIMULATED</u>	8.6	7.5
Diltiazem	Moderate inhibitor	<u>SIMULATED</u>	5.5	5.0
Rifampin	Strong inducer	Observed	0.08	0.06
Efavirenz	Moderate inducer	<u>SIMULATED</u>	0.38	0.38

Slide courtesy of Vikram Sinha, (Office of Clin. Pharmacology, CDER, FDA) at MISG Forum, ABPI, MHRA 2014.

Number of Compounds Assessed Using Absorption Modelling in the OGD, CDER, US FDA



Slide courtesy of L. Zhao (OGD, CDER, FDA; May 2016)

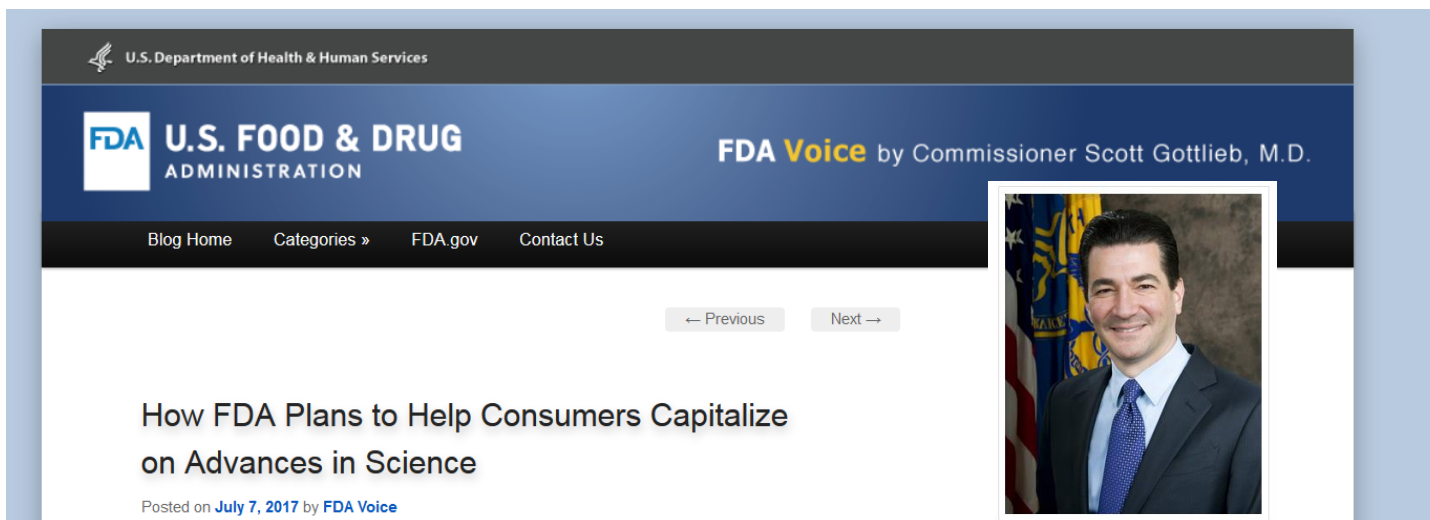
Application areas in the OGD, CDER, US FDA (2008-2016)

Category	Potential Applications	Current Status
Dissolution Method and Acceptance Criteria	Justify/support bio-predictive dissolution method	<ul style="list-style-type: none"> Use the verified PBPK/absorption model combined with bioequivalence clinical study and dissolution profiles generated <u>to show that the proposed dissolution method can reject non-BE (bioequivalence) batch</u>
	Set clinically relevant dissolution acceptance criteria	<ul style="list-style-type: none"> Allow dissolution <u>acceptance criteria to go beyond target $\pm 10\%$ range</u> Additional evidence (data) needed to validate model and confirm predictive performance
Set clinically relevant drug product specifications for CMAs and CPPs	CMAs (particle size, polymorphic form)	<ul style="list-style-type: none"> <u>Predict particle size distribution (PSD) limits</u> which would result in similar in vivo performance to the target (clinical batch) <u>Predict the effect of polymorphic form</u> on in vivo performance of drug product
	CPPs (milling method, pressure force/hardness)	<ul style="list-style-type: none"> <u>Predict the effect of milling method</u> on the bioequivalence of drug product (e.g. pre- and post-change of milling method) <u>Justify specification range of compression force</u> based on the predicted in vivo performance
Risk assessment	Evaluation of the risk	<ul style="list-style-type: none"> <u>Quantitative</u> assessment

Slide courtesy of L. Zhao (OGD, CDER, FDA; May 2016)

FDA Voice by Commissioner

FDA Voice blog: July 7th, 2017



Today we announced our detailed work plan for the steps we're taking to implement different aspects of Cures. I want to highlight one example of these steps, which we're investing in, and will be expanding on, as part of our broader Innovation Initiative. It's the use of in silico tools in clinical trials for improving drug development and making regulation more efficient.

To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don't want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don't add to our understanding of the product's safety and benefits.

FDA's Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms. We'll be putting out additional, updated guidance on how aspects of these in silico tools can be advanced and incorporated into different aspects of drug development.

FDA reviewers/scientists continue to publish/present their internal research

RESEARCH ARTICLE – Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Application of Physiologically Based Absorption Modeling for Amphetamine Salts Drug Products in Generic Drug Evaluation

ANDREW H. BABISKIN, XINYUAN ZHANG

Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland 20993

Received 30 January 2015; revised 8 April 2015; accepted 9 April 2015

Using M&S to predict virtual BE and assess dissolution specifications (Babiskin et al., 2015)

Keywords: physiological model; absorption; bioequivalence; bioavailability; clinical trial simulation; modified release

Integrating in vitro, modeling, and in vivo approaches to investigate warfarin bioequivalence

Xinyuan Zhang^{1,*}, Hong Wen^{1,*}, Jianghong Fan^{1,*}, Bradley Vince², Tonglei Li³, Wei Gao³, Minori Kinjo^{1,*}, Jill Brown^{4,*}, Wanjie Sun^{4,*}, Wenlei Jiang^{1,*}, and Robert Lionberger^{1,*}

¹ Office of Generic Drugs, Food and Drug Administration, Silver Spring, MD

² Vince and Associates Clinical Research, LLC, Silver Spring, MD

³ Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN

⁴ Office of Translational Sciences, Food and Drug Administration, Silver Spring, MD

Virtual BE trial simulations for warfarin (Zhang et al., 2017)

Research Article

Utility of Physiologically Based Absorption Modeling in Implementing Quality by Design in Drug Development

Xinyuan Zhang,¹ Robert A. Lionberger,^{1,2} Barbara M. Davit,¹ and Lawrence X. Yu¹

Received 16 September 2010; accepted 14 December 2010; published online 5 January 2011

Abstract. To implement Quality by Design (QbD) in drug development, scientists need tools that link drug product properties to *in vivo* performance. Physiologically based absorption models are potentially useful tools; yet, their utility of QbD implementation has not been discussed or explored much in the literature. We simulated pharmacokinetics (PK) of carbamazepine (CBZ) after administration of four oral formulations, immediate-release (IR) suspension, IR tablet, extended-release (XR) tablet and capsule, under fasted and fed conditions and presented a general diagram of a modeling and simulation strategy integrated with pharmaceutical development. We obtained PK parameters and absorption scale factors (ASFs) by deconvolution of PK data validated for other PK products. We explored three key areas we used to help identify optimal critical formulation variables for the IR tablet that showed decreased. Finally, virtual bioequivalence studies showed that a predictive model is a potential tool for QbD implementation. **KEY WORDS:** advanced drug release (MR); quality by design (QbD).

Incorporating M&S to assist with Quality by Design (QbD) (Zhang et al., 2011)

RESEARCH PAPER

Use of In Vitro–In Vivo Correlation to Predict the Pharmacokinetics of Several Products Containing a BCS Class I Drug in Extended Release Matrices

Tahseen Mirza, Srikant A. Byladi, Christopher D. Elson, Yongheng Wang, Barbara M. Davit, Manoor A. Khan

Received: 29 February 2012 / Accepted: 9 August 2012
© Springer Science+Business Media, LLC 2012

ABSTRACT

Purpose To determine if an IVVC model can predict PK profiles of varying formulations of a BCS Class I drug that is a salt of a weak base. **Method** An MVC model (Level A) was created by combining deconvoluted *in vivo* absorption data obtained from oral administration of 50 mg, 100 mg, and 200 mg fast and slow extended release formulations with *in vitro* percent dissolved using residual regression analysis. The model was then used to predict the *in vivo* profile of the test products that varied in formulation characteristics. **Results** The model passed internal validation for predicted C_{max} and AUC. For external validation, *in vitro* data of five different test formulations was utilized. The model passed external validation for two test formulations that were different but belonging to the same release mechanism as that of the reference formulation. Three formulations failed external validation because they belonged to either a mixed or different release mechanism. The model and results were further confirmed.

ABBREVIATIONS

AUC area under the curve
BCS biopharmaceutics classification system
 C_{max} maximum drug concentration observed in the blood/plasma profile
FRA fraction of drug absorbed into the body
FRD fraction of drug dissolved during *in vitro* experimentation
IVVC *in vitro*–*in vivo* correlation
 k_e constant of elimination
MAPE mean absolute percentage error
rpm revolutions per minute
SURF-MR scale up post approval changes modified release
 V_d volume of distribution
 $\%PE_{AUC}$ percent error of AUC prediction
 $\%PE_{C_{max}}$ percent error of C_{max} prediction

INTRODUCTION

In vitro–*in vivo* correlation (IVVC) has been defined by the United States Pharmacopeia (USP) Subcommittee on Biopharmaceutics as “the establishment of a rational relationship between a biological property, or parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form” (1). The Food and Drug Administration defines IVVC as “A predictive mathematical model describing the relationship between an *in vitro* property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed” (2). In most cases, the *in vitro* property is the rate or extent of drug dissolution or release while the *in vivo* response is the plasma drug concentration.

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Division of Biopharmaceutics II (CDER/OP/SD/CD/DR)
7510 Standish Place
Rockville, Maryland 20855, USA

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- John DiBella, Simulations Plus Inc.
- Aditya Marfatia, Electrolab.

Thank You

Back-up slides

GastroPlus™ user interface: Compound

GastroPlus(TM): GastDemo.mdb (C:\Users\Public\Simul..\Gastr..\)

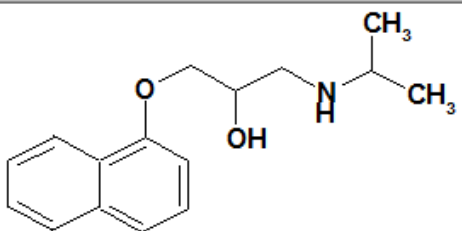
File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Gut Physiology-Hum Pharmacokinetics Simulation Graph

Selected Compound

Propranolol HCl

Current= 1; Total = 9



Molecular Formula: C16H21NO2
 Molecular Weight (g/mol): 259.34
 Reference logD: 1.54 @pH: 7.4

pKa Table
 Enzyme Table
 Transporter Table

ver. 9.5.0008
 SI Trans Time (h) = 3.228 Mean Abs Time (h) = 0.562
 Longest Diss. Time (h) is @ pH 1.0 = 0.001 hours
 Max Abs Dose (S+) = 1.194E+6 mg Max Abs Dose (lit) = 7.52E+5 mg
 Support Files
 Propranolol HCl.opd

Dosage Form: IR: Tablet

Initial Dose (mg): 140.28
 Subsequent Doses (mg): 0
 Dosing Interval (h): 0
 Dose Volume (mL): 250
 pH for Reference Solubility: 3
 Solubility (mg/mL @pH=3): 125
 Mean Precipitation Time (sec): 900
 Diff. Coeff. (cm²/s x 10⁻⁵): 0.829
 Drug Particle Density (g/mL): 1.2
 Particle Size: R=25.00, D=50.00

Effective Permeability

Source: Human

Peff (cm/s x 10⁴): 2.91
 Sim Peff x10⁴ (Human) 2.91

Convert from User Data

Biorelevant Solubilities

Dose No. = 0.0309

Absorption No. = 5.741

Dissolution No. = 4.817E+3

Biorelevant solubilities from ADMET Predictor v6.1

pKa Table | logD: Struct-6.1 | Diss Model: Johnson | PartSize-Sol: ON | BileSalt-Sol: ON | Diff: ON | ConstRad: ON | Precip: Time | Ppara: OFF | EHC: OFF

GastroPlus™ user interface: Gut Physiology

GastroPlus(TM): GastDemo.mdb (C:\Users\Public\Simul..\Gastr..)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound **Gut Physiology-Hum** Pharmacokinetics Simulation Graph

Compartmental Parameters

Propranolol HCl Excrete all un-absorbed drug at the end of gut transit time
 Zero-order gastric emptying

Compartment Data										Enzyme and Transporter Regional Distributions
Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)	
Stomach	0	0.0	1.30	0.25	48.92	29.19	9.87	1.000	0.0	
Duodenum	0	2.727	6.00	0.26	44.57	14.58	1.56	4.235	2.800	
Jejunum 1	0	2.678	6.20	0.94	166.6	60.26	1.48	3.949	2.330	
Jejunum 2	0	2.675	6.40	0.74	131.0	60.26	1.32	3.489	2.030	
Ileum 1	0	2.640	6.60	0.58	102.0	60.26	1.16	3.029	1.410	
Ileum 2	0	2.621	6.90	0.42	75.35	60.26	1.00	2.569	1.160	
Ileum 3	0	2.589	7.40	0.29	53.57	60.26	0.84	2.109	0.140	
Caecum	0	0.352	6.40	4.36	50.49	13.50	3.45	1.790	0.0	
Asc Colon	0	0.823	6.80	13.07	53.55	28.35	2.45	2.480	0.0	

C1-C4:

Physiology:

ASF Model:

Qh (L/min):

Percent Fluid in SI: Colon:

Biorelevant solubilities from ADMET Predictor v6.1

pKa Table | logD: Struct-6.1 | Diss Model: Johnson | PartSize-Sol: ON | BileSalt-Sol: ON | Diff: ON | ConstRad: ON | Precip: Time | Ppara: OFF | EHC: OFF

GastroPlus™ user interface: Pharmacokinetics

GastroPlus(TM): GastDemo.mdb (C:\Users\Public\Simul.\Gastr.\)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Gut Physiology-Hum **Pharmacokinetics** Simulation Graph

PK Parameters

PK Model: Compartmental

Body Weight (kg): 74

FPE (if fixed) [%]

Oral:	0	Intestinal:	0	Liver:	61.84
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Blood/plasma Conc Ratio: 0.75

Use Exp Plasma Fup [%]: 9

Use Adj Plasma Fup [%]: 8.8323

Renal Clearance CLr (L/h/kg): 0

CL (L/h): 0 or (L/h/kg): 0.75215

Vc (L/kg): 2.91

T 1/2 (h): 4.31

K12 (1/h): 0.291 K13 (1/h): 0

K21 (1/h): 0.641 K31 (1/h): 0

V2 (L/kg): 1.3211 V3 (L/kg): 0

Observed Values

Fa %:	94	CMax (µg/mL):	0
FDp %:	0	TMax (h):	2
F %:	35	AUCinf (ng-h/mL):	0
		Hepatic Clearance (L/h):	0

Propranolol HCl

Metabolism/Transporter Scale Factors

Enzymes	Gut		Liver	
	Vmax SF:	Km SF:	Vmax SF:	Km SF:
	1	1	1	1

Gut Transporters	Apical		Basolateral	
	Influx Vmax SF:	Influx Km SF:	Efflux Vmax SF:	Efflux Km SF:
	1	1	1	1

Transfer SFs to Enz/Trans tables Liver Enzyme Turnover Rates

Biorelevant solubilities from ADMET Predictor v6.1

pKa Table | logD: Struct-6.1 Diss Model: Johnson PartSize-Sol: ON BileSalt-Sol: ON | Diff: ON ConstRad: ON Precip: Time Ppara: OFF EHC: OFF

GastroPlus™ user interface: Simulation

GastroPlus(TM): GastDemo.mdb (C:\Users\Public\Simul..\Gastr..)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Gut Physiology-Hum Pharmacokinetics **Simulation** Graph

Simulation Mode

Single Simulation PSA
 Batch Simulation Population Simulator

Stop Start

Single Simulation Input

Simulation Length (h):

Single Simulation Output

Simulation Time Elapsed (h):

	Obs	Calc
Fa %:	<input type="text"/>	<input type="text"/>
FDp %:	<input type="text"/>	<input type="text"/>
F %:	<input type="text"/>	<input type="text"/>
CMax (ug/mL):	<input type="text"/>	<input type="text"/>
TMax (h):	<input type="text"/>	<input type="text"/>
AUC 0-inf (ug-h/mL):	<input type="text"/>	<input type="text"/>
AUC 0-t (ug-h/mL):	<input type="text"/>	<input type="text"/>
CMaxLiv (ug/mL):	<input type="text"/>	<input type="text"/>

Propranolol HCl

Figure (c) Capsugel

Biorelevant solubilities from ADMET Predictor v6.1

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GastroPlus™ user interface: Graph

