sparc

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

Anant Ketkar, Ph.D.

Sun Pharma Advanced Research Company Ltd., Mumbai

SPDS 6th International Annual Symposium on Dissolution Science and Applications

28th & 29th June, 2018, Hyderabad.

ELECTROLAB SimulationsPlus | Cognigen | DILIsym Services
SCIENCE+SOFTWARE=SUCCESS

Contents

- Introduction to PBPK Modelling and Simulation
- IVIVR/IVIVC: Traditional Vs PBPK approach
- Case Studies
- Regulatory acceptance
- Acknowledgements

Disclaimer:

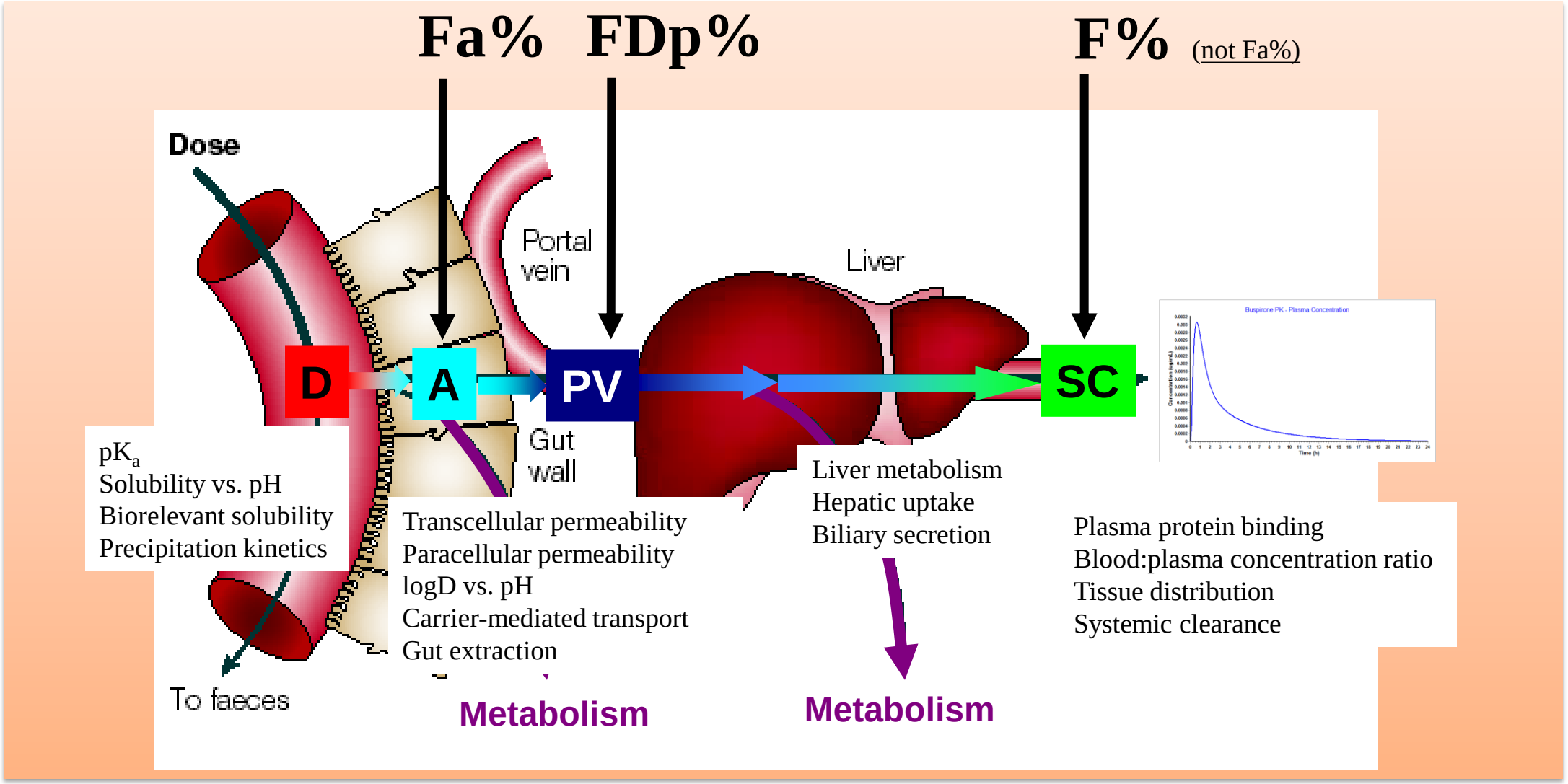
"The opinions expressed in this presentation are solely those of the presenter and not necessarily those of SPARC. SPARC does not guarantee the accuracy or reliability of the information provided herein."

Introduction to PBPK Modelling and Simulation

PBPK M&S ?

- **P**hysiologically **B**ased **P**harmaco**k**inetic **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)

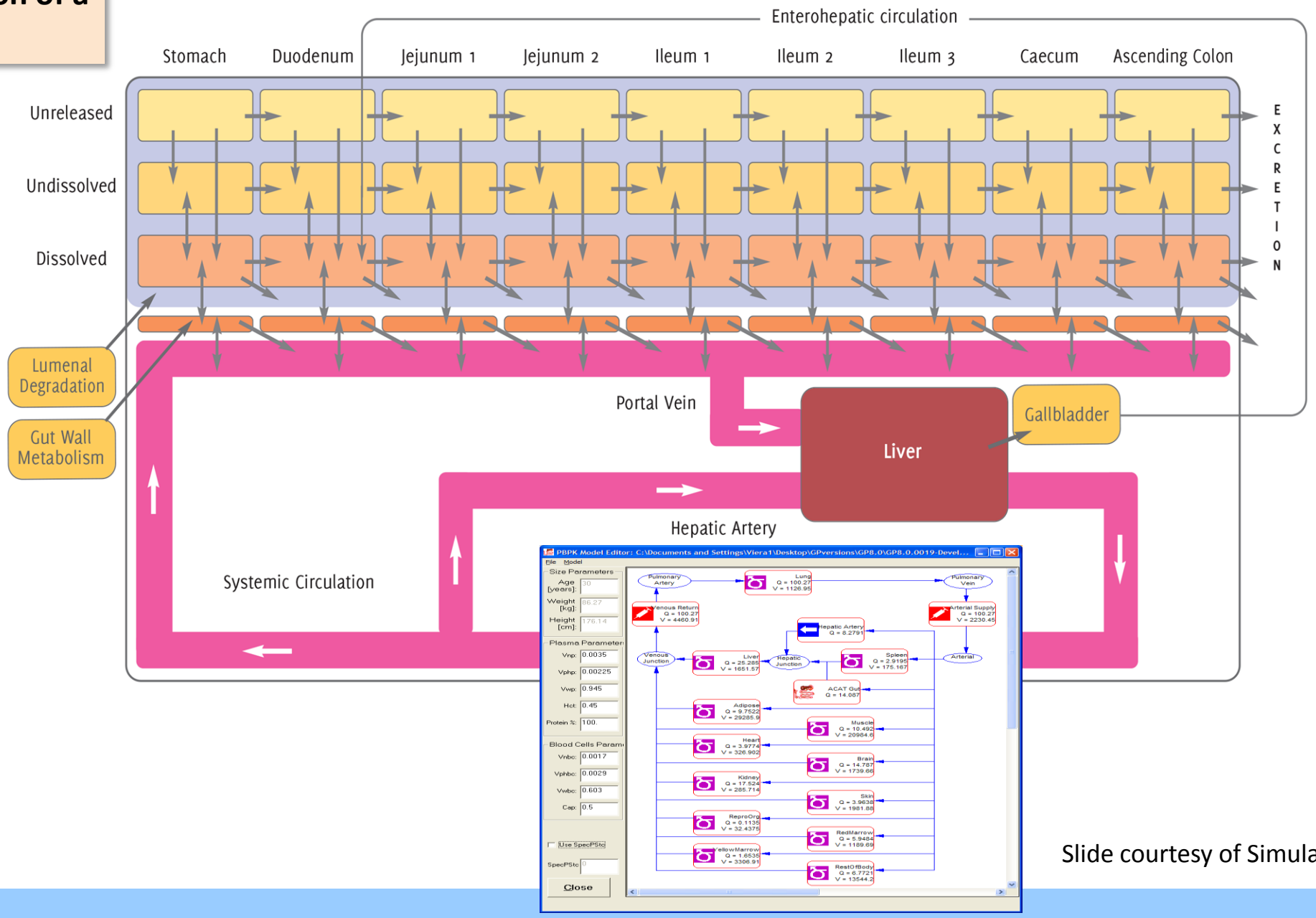
What's happening in vivo? (after oral administration)



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

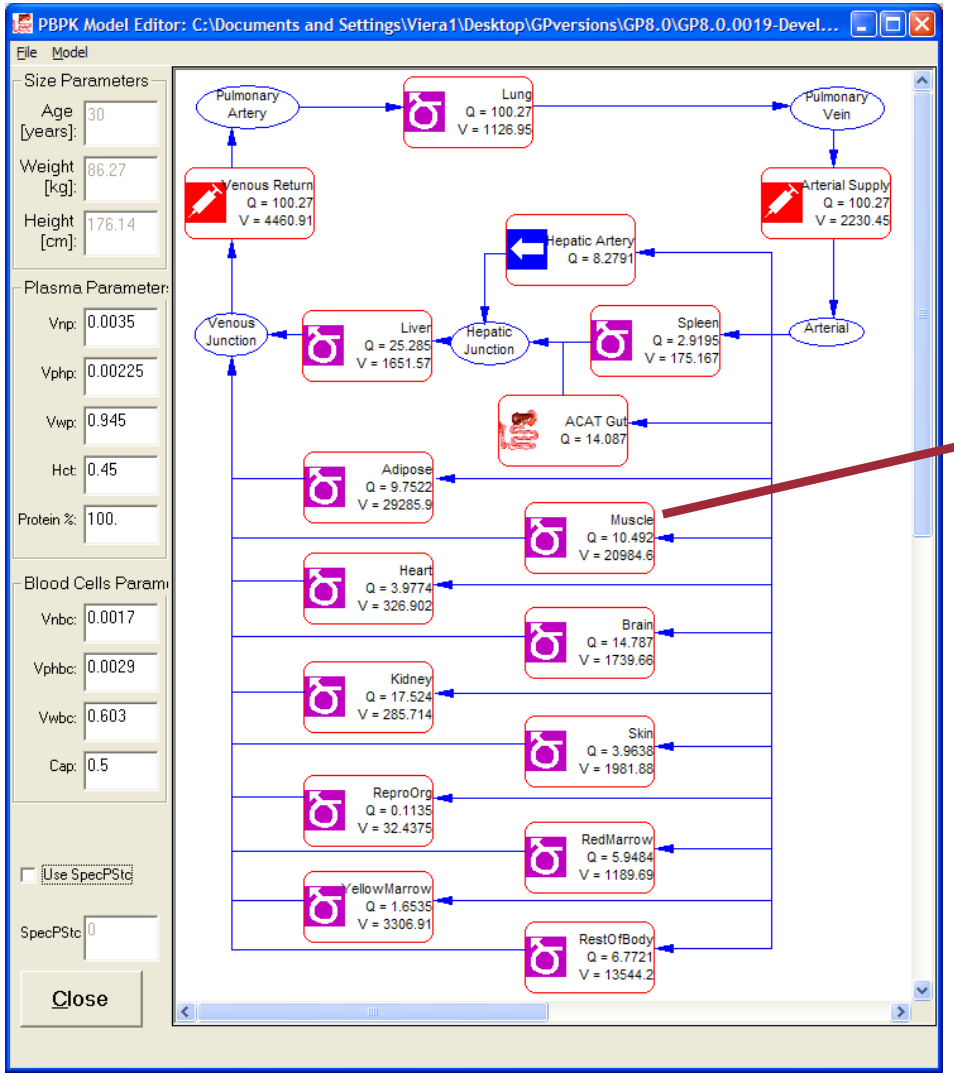
Schematic representation of a PBPK model

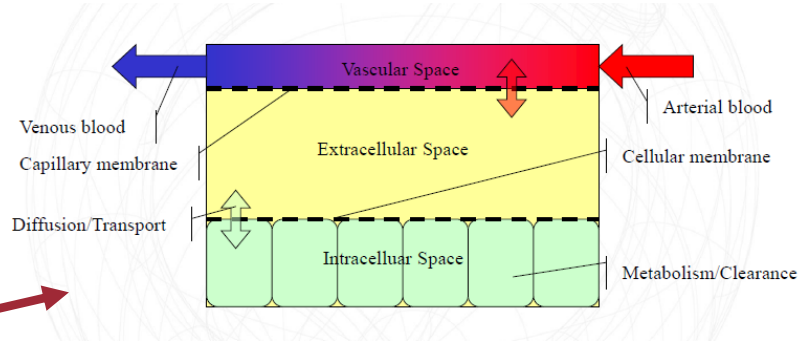
Advanced Compartmental Absorption and Transit Model (ACAT™)



Slide courtesy of Simulations Plus Inc.

What's defined in a PBPK model?





$$Vt\frac{dCt}{dt} = \left(Q \times Cbi - \frac{Q \times Ct \times R_{bp}}{Kp} - CL_{int,u}\left(\frac{Ct \times fu_p}{Kp}\right)\right)$$

- 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)

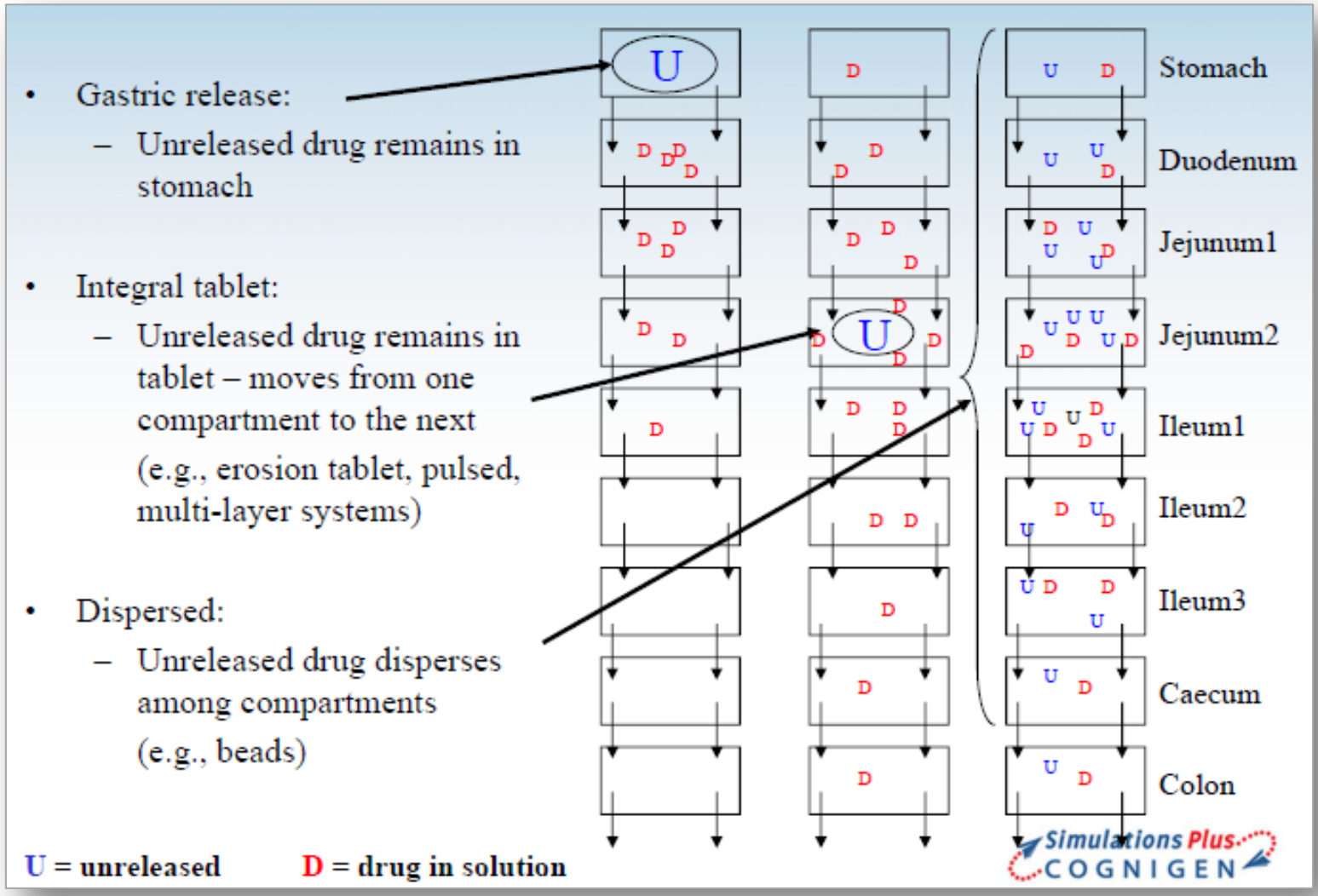
Slide courtesy of Simulations Plus Inc.

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

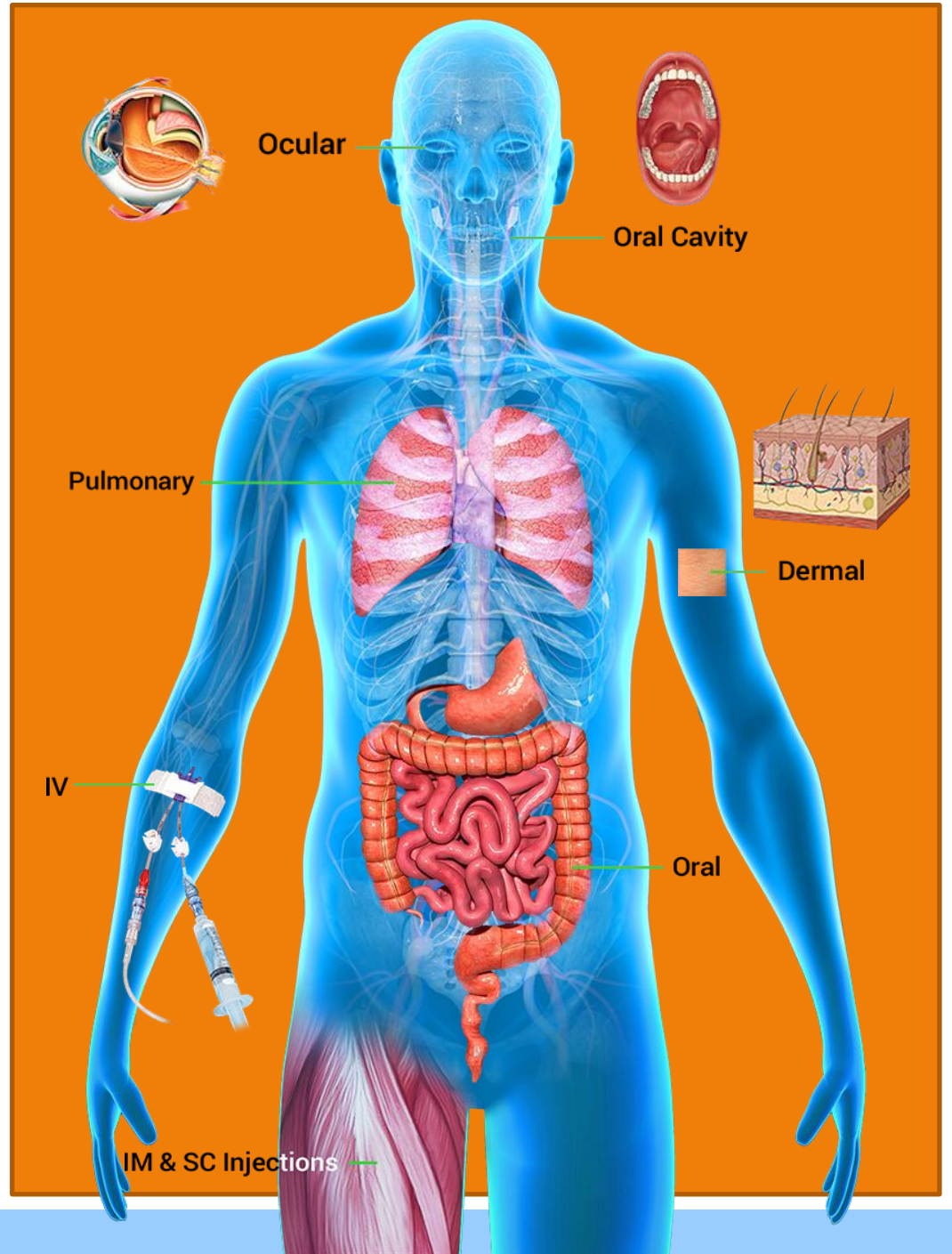
- Gastric release:
  - Unreleased drug remains in stomach
- Integral tablet:
  - Unreleased drug remains in tablet – moves from one compartment to the next (e.g., erosion tablet, pulsed, multi-layer systems)
- Dispersed:
  - Unreleased drug disperses among compartments (e.g., beads)



Slide courtesy of Simulations Plus Inc.

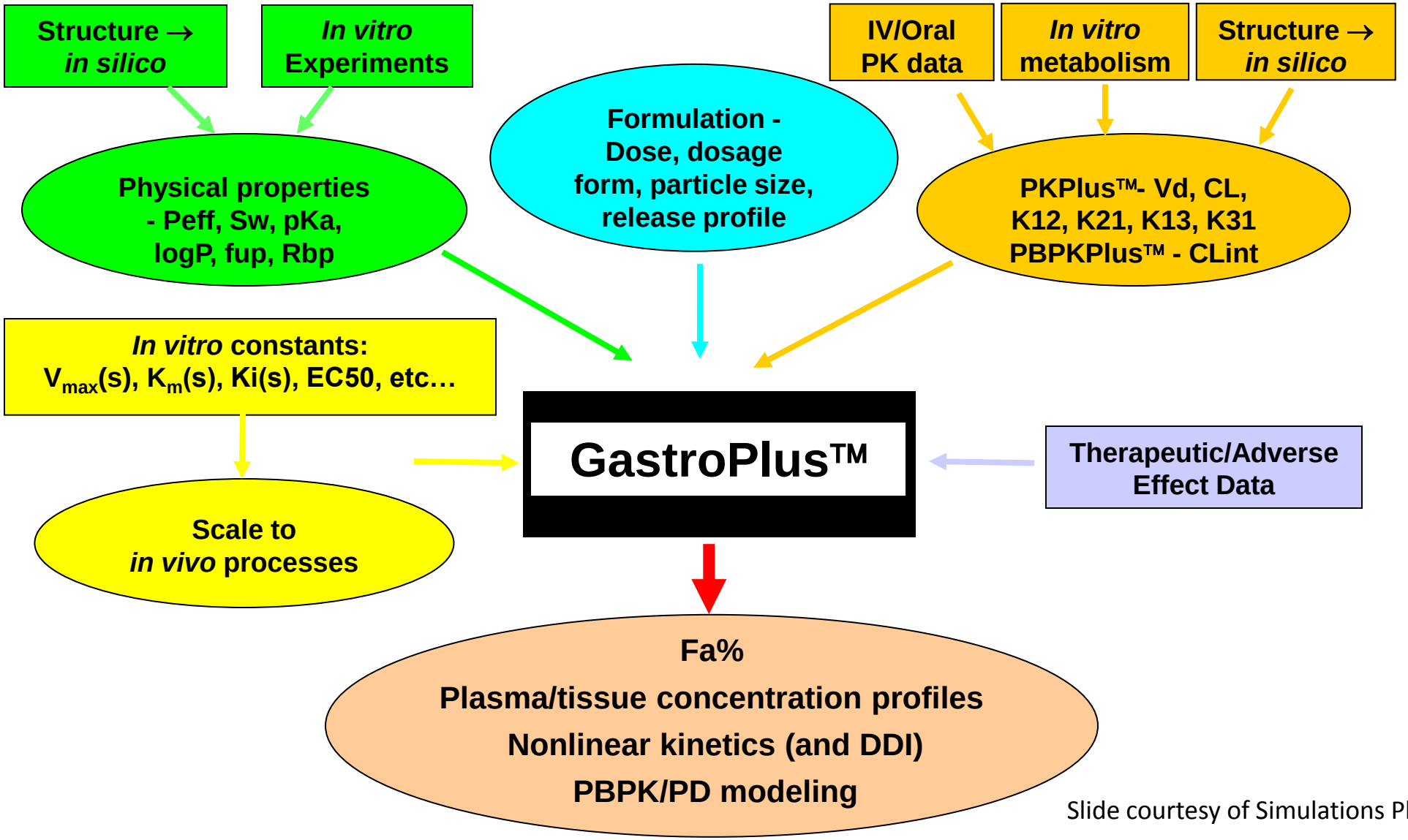
Other routes

- 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.

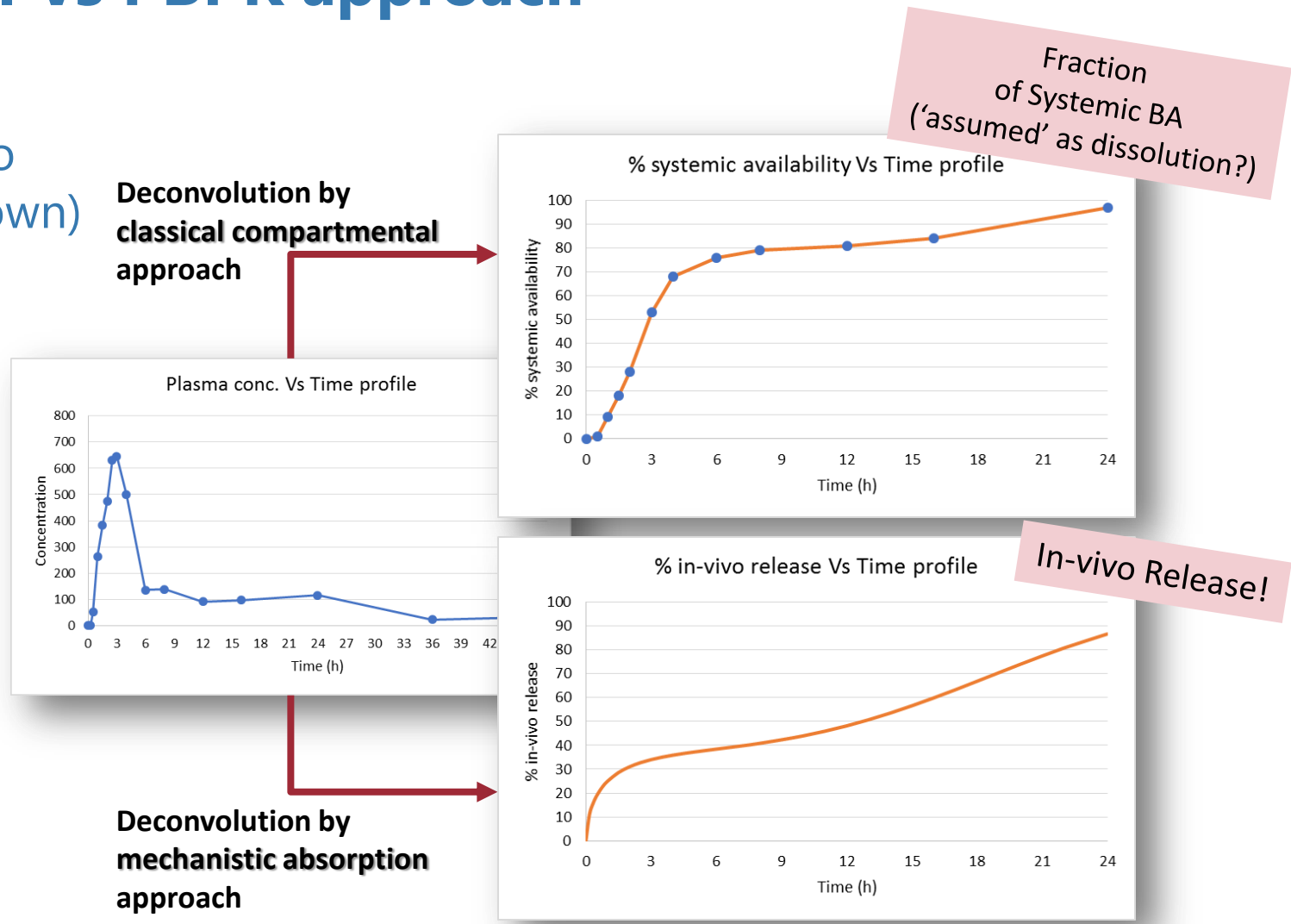
IVIVR/IVIVC: Traditional Vs PBPK approach

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

Slide courtesy of Simulations Plus Inc.

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 (Peff, ADMET Predictor 8.1): ~4.0 x 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 ~85%.
- PBPK Modelling platform: GastroPlus™ 9.5

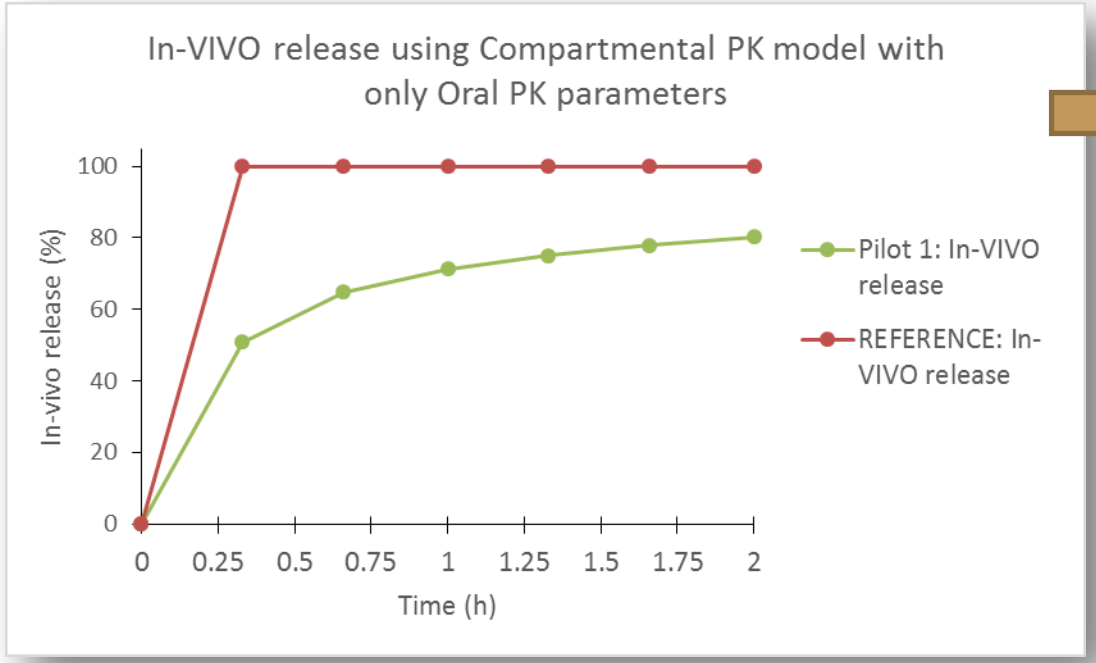
Case Study 1: Effect of PK modelling approach (contd.)

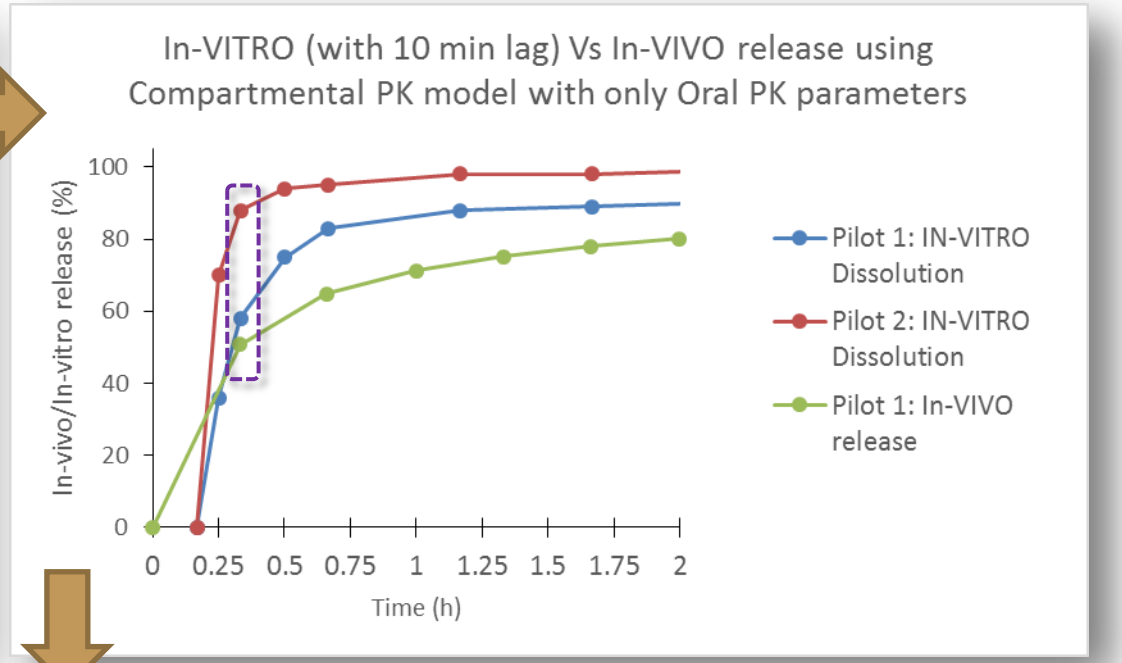
- Results of 1st pilot PK study

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).
- Vd 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.)

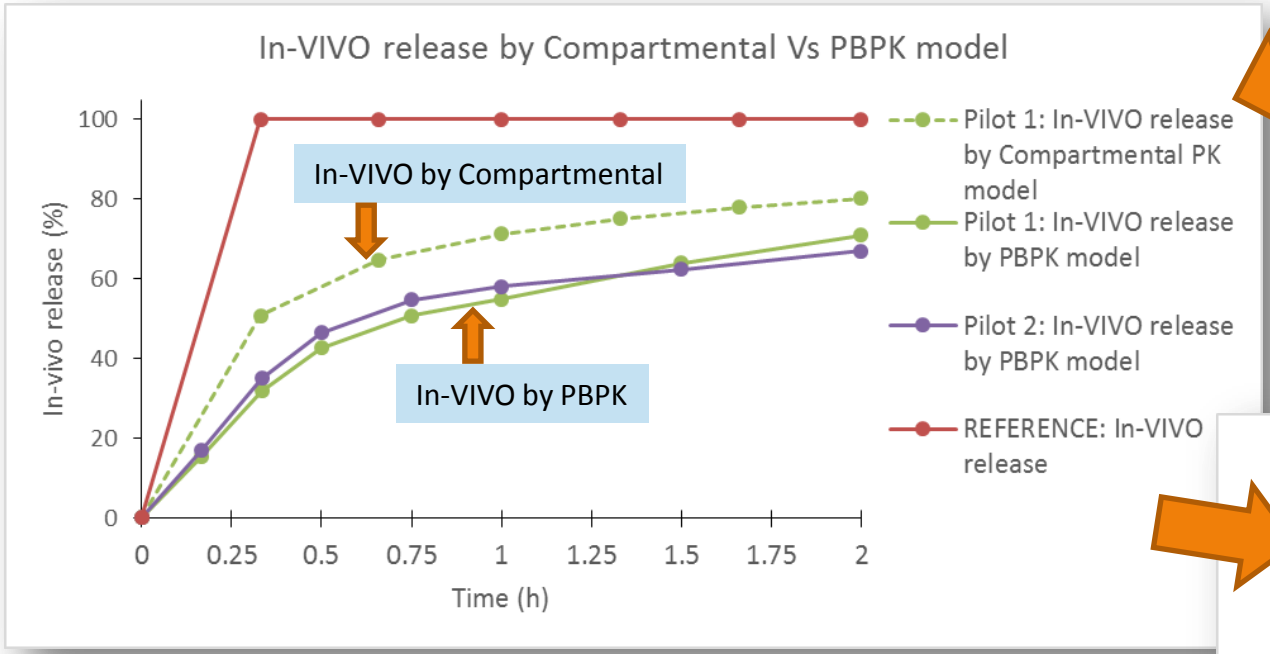
- Results of 2nd pilot PK study

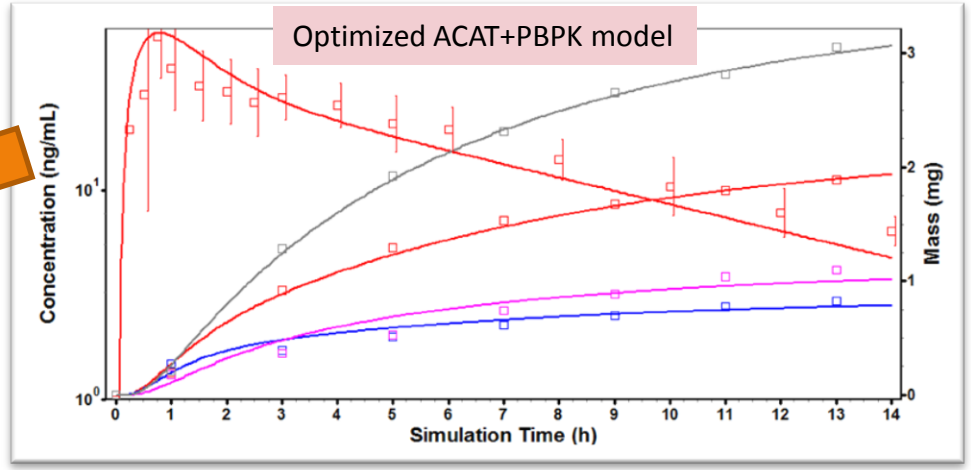
PK Parameter	Pilot #1	Pilot #2
C_{max}	67%	70%
AUC_{0-t}	102%	99%

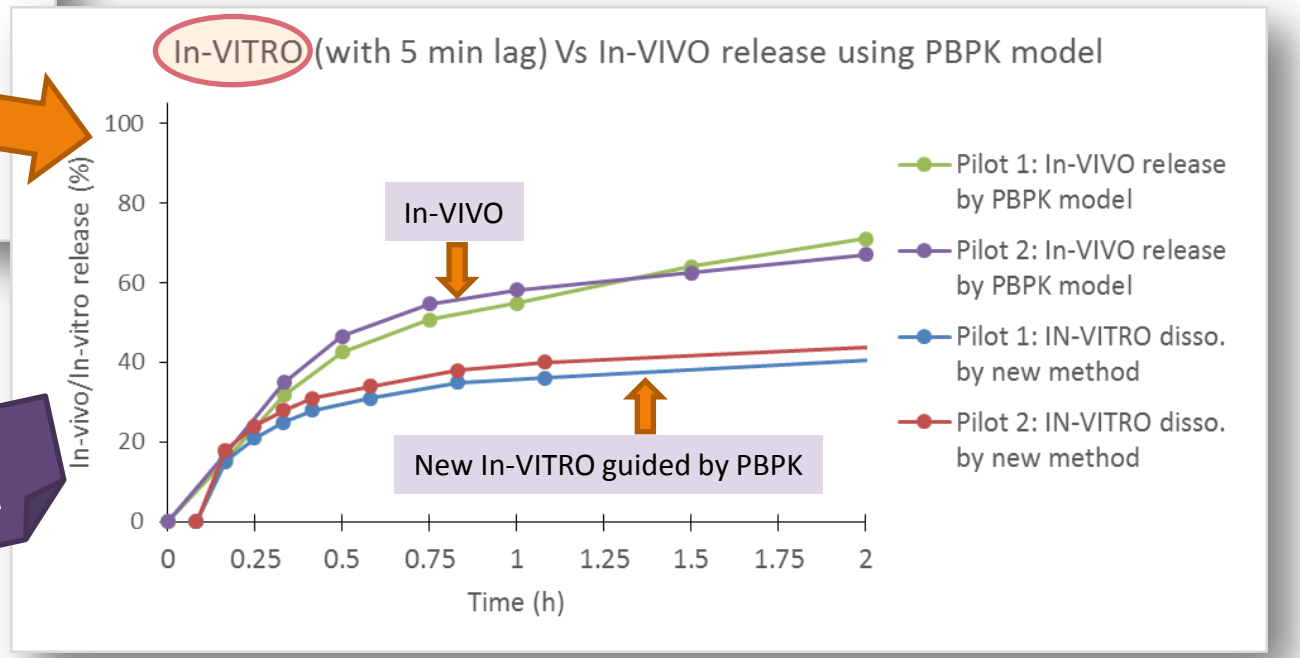
only ~3% rise in the ratio!!!

- Dissolution method was guided by PK model
  - Absence of true estimates of Vd 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
  - Vd 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.)







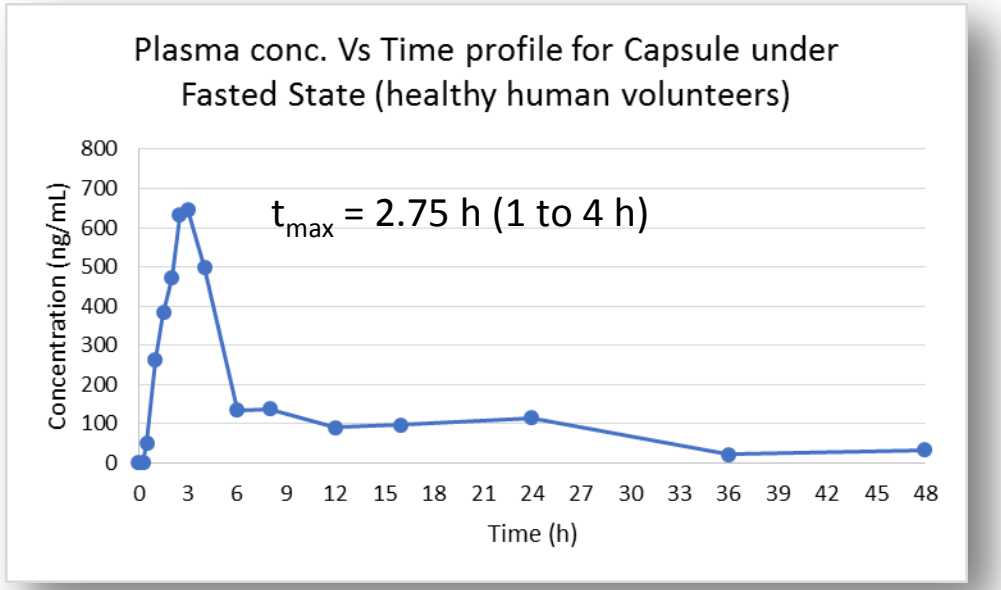
Better confidence in new in-VITRO method

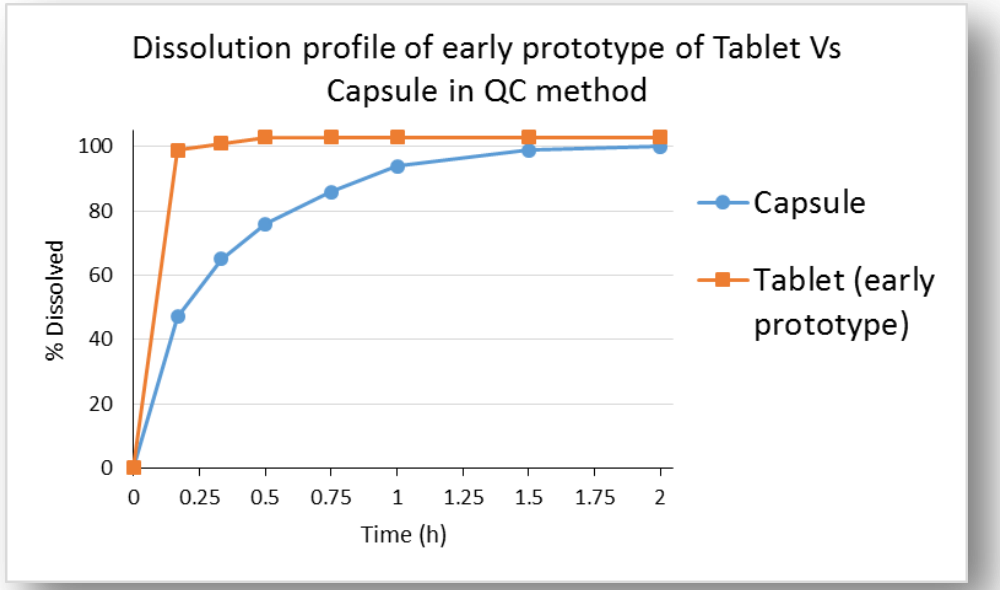
Case Study 2: Formulation switch for a NCE

- 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.)

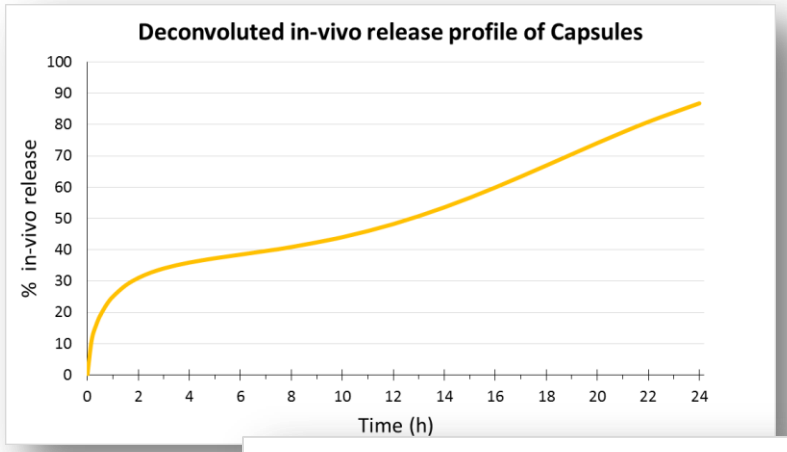
- Does the capsule release complete drug in-vivo?
- Is there any possibility of in-vivo precipitation?
- Is the QC method under/over discriminatory?

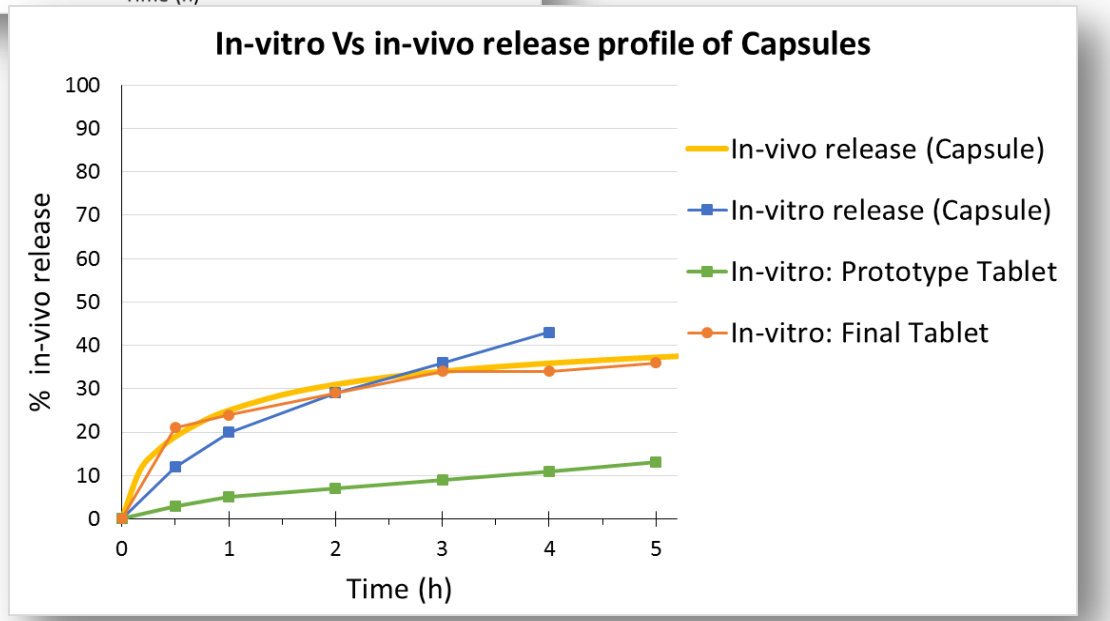




Case 2: Formulation switch for a NCE (contd.)

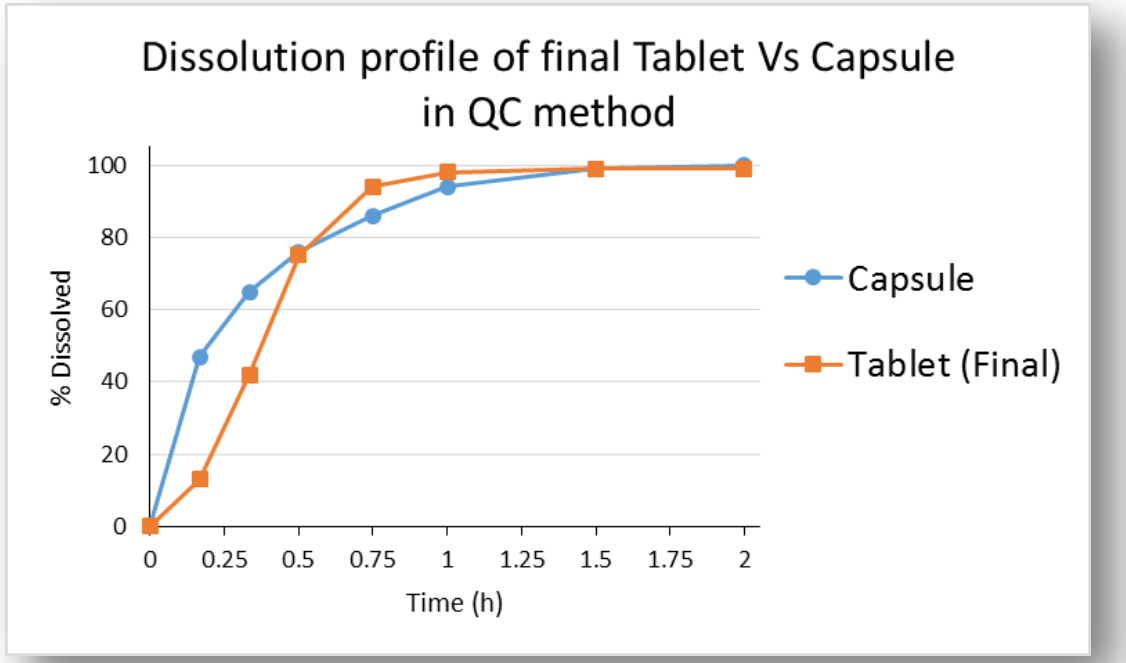
- Mechanistic deconvolution based on ACAT coupled with PBPK modelling
  - In-vivo precipitation followed by slow and sustained dissolution
  - C_{max} is resulting from dissolution of only 20-40% of drug
- Bio-relevant dissolution method
  - Non-sink conditions
  - Optimization of tablet formulation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

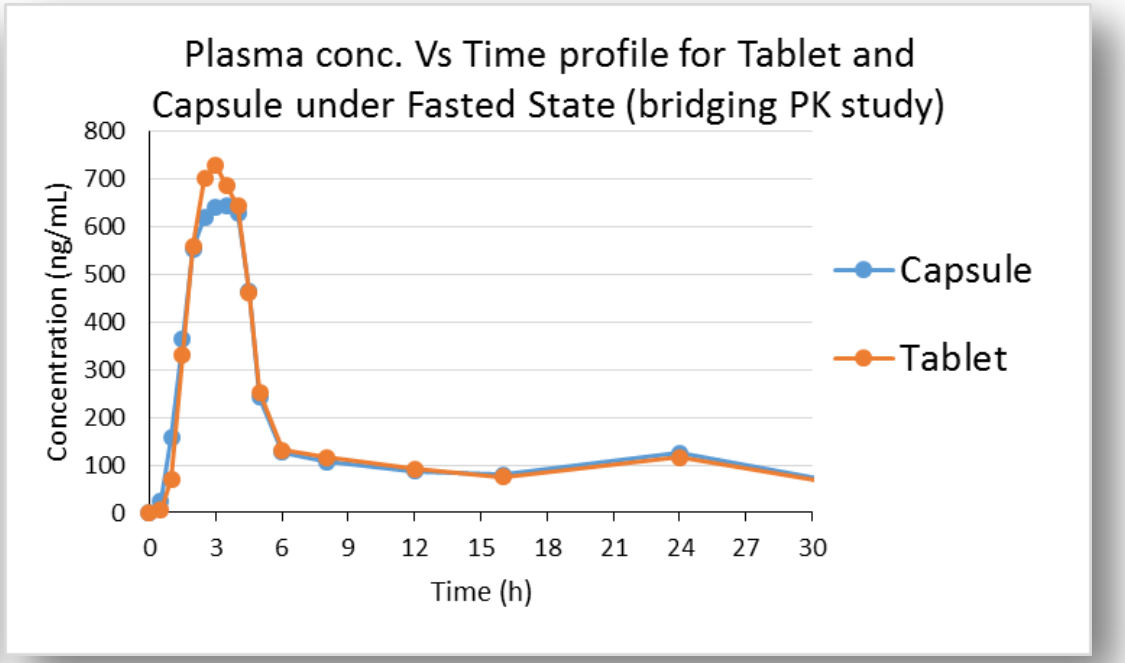




Case 2: Formulation switch for a NCE (contd.)

- 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

Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

DRAFT GUIDANCE

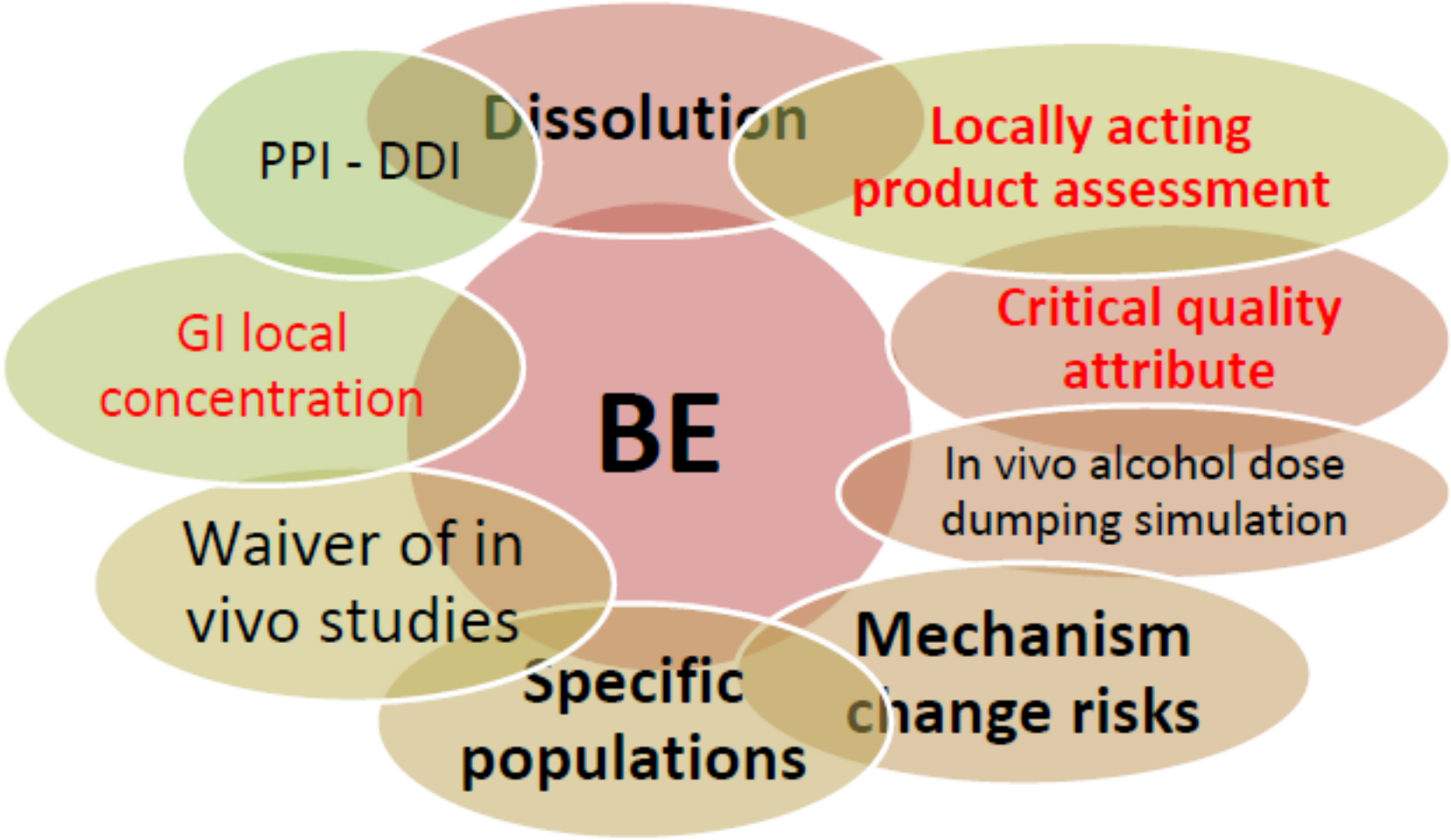
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2016
Clinical Pharmacology

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

….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



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

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

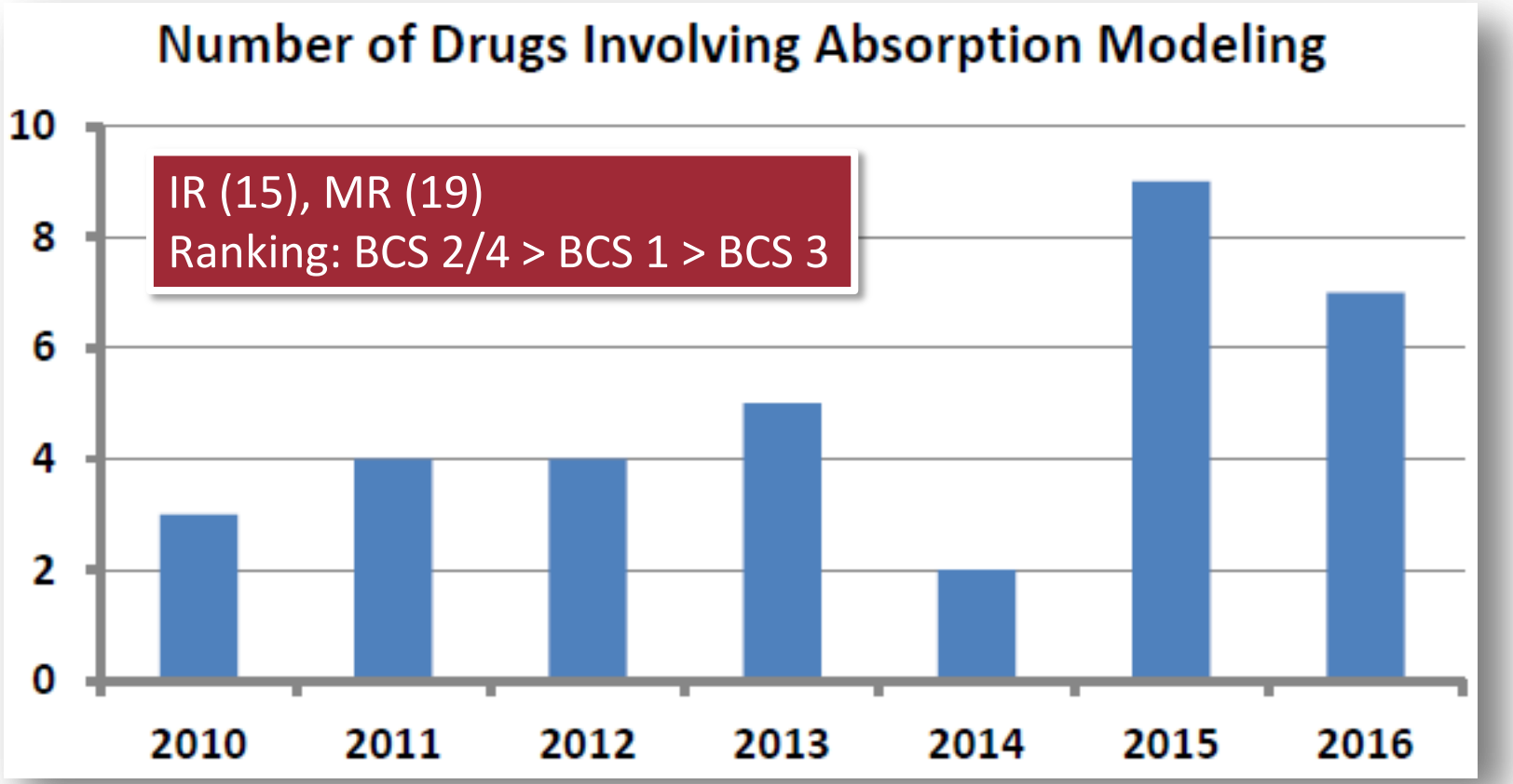
Highlights of PBPK M&S Impacts (Year 2016) in the OGD, CDER, US-FDA

- 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	SIMULATED	8.6	7.5
Diltiazem	Moderate inhibitor	SIMULATED	5.5	5.0
Rifampin	Strong inducer	Observed	0.08	0.06
Efavirenz	Moderate inducer	SIMULATED	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)

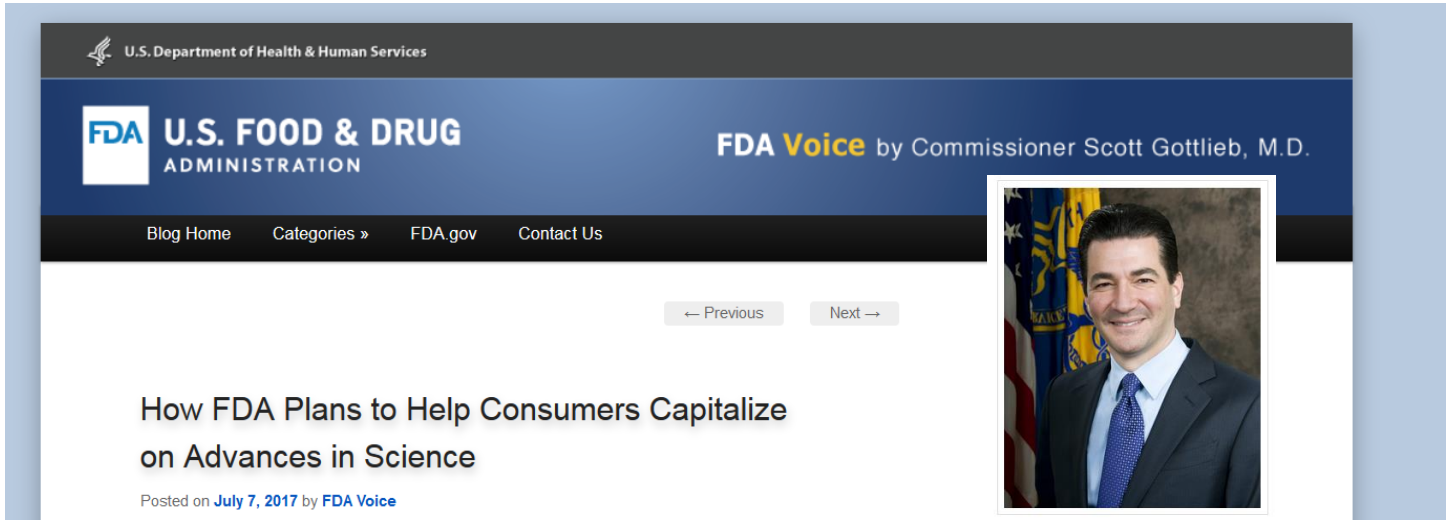
Application areas in the OGD, CDER, US FDA (2008-2016)

Category	Potential Applications	Current Status
Dissolution Method and Acceptance Criteria	Justify/support **bio-predictive dissolution method**	• Use the verified PBPK/absorption model combined with bioequivalence clinical study and dissolution profiles generated to show that the proposed dissolution method can reject non-BE (bioequivalence) batch
	Set **clinically relevant dissolution acceptance criteria**	• Allow dissolution acceptance criteria to go beyond target ±10% range • 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)	• Predict particle size distribution (PSD) limits which would result in similar in vivo performance to the target (clinical batch) • Predict the effect of polymorphic form on in vivo performance of drug product
	CPPs (milling method, pressure force/hardness)	• Predict the effect of milling method on the bioequivalence of drug product (e.g. pre- and post-change of milling method) • Justify specification range of compression force based on the predicted in vivo performance
Risk assessment	**Evaluation of the risk**	• Quantitative 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)

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. Yu[1]

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

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. Bykadi • Christopher D. Ellison • Yongheng Yang • Barbara M. Davit • Mansoor A. Khan

Received: 28 February 2012 / Accepted: 9 August 2012

Generating mechanistic IVIVCs to predict test formulations

(Mirza et al., 2012)

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

Xinyuan Zhang[1,*,§], Hong Wen[1,*], Jianghong Fan[1,*], Bradley Vince[2], Tonglei Li[3], Wei Gao[3], Minori Kinjo[1,*], Jill Brown[4,*], Wanjie Sun[4,*], Wenlei Jiang[1,*], and Robert Lionberger[1,*]

[1] Office of Generic Drugs, Food and D

[2] Vince and Associates Clinical Resear

[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)

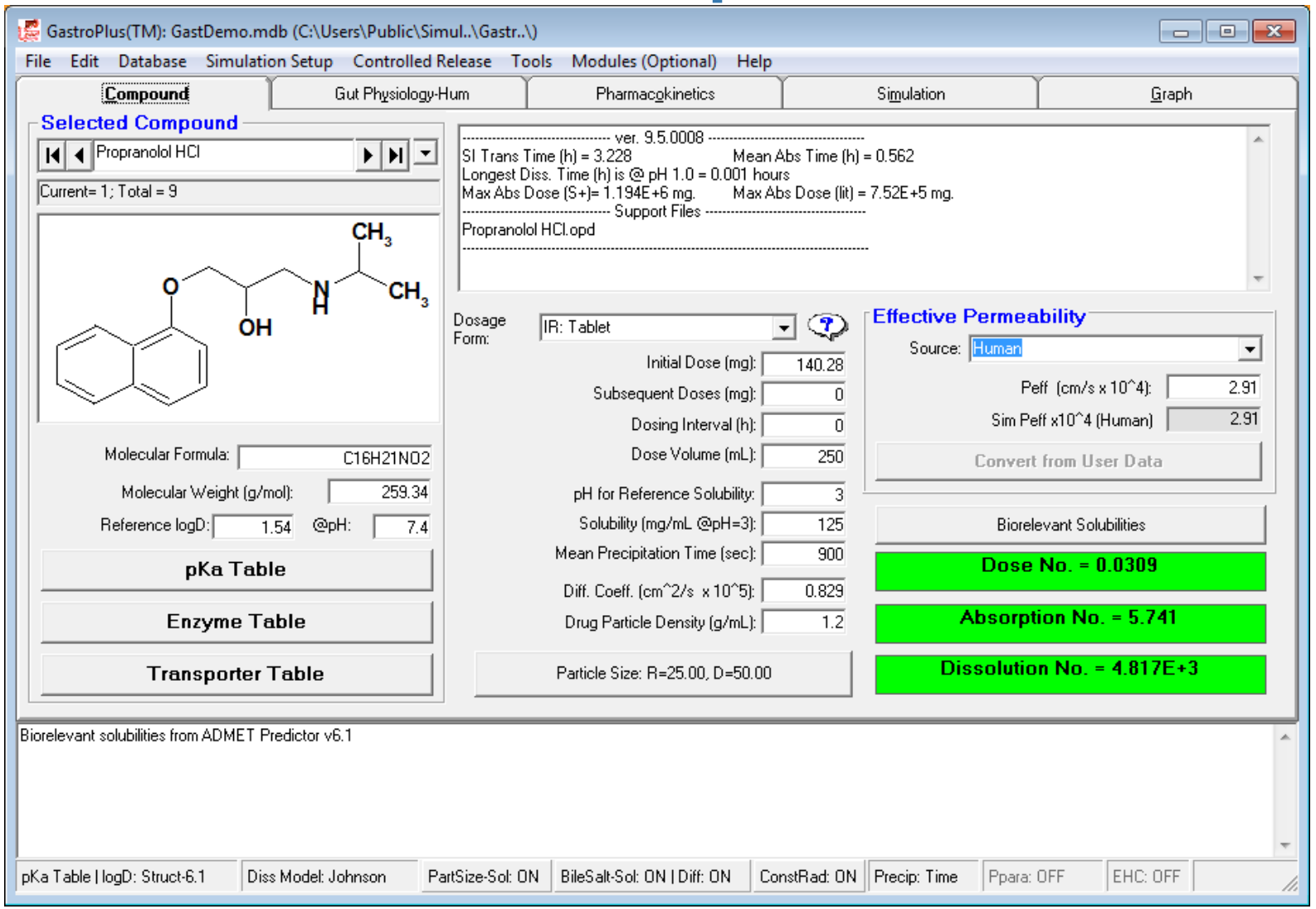
Acknowledgements

- Formulation and Analytical Development colleagues, SPARC.
- John DiBella, Simulations Plus Inc.
- Aditya Marfatia, Electrolab.

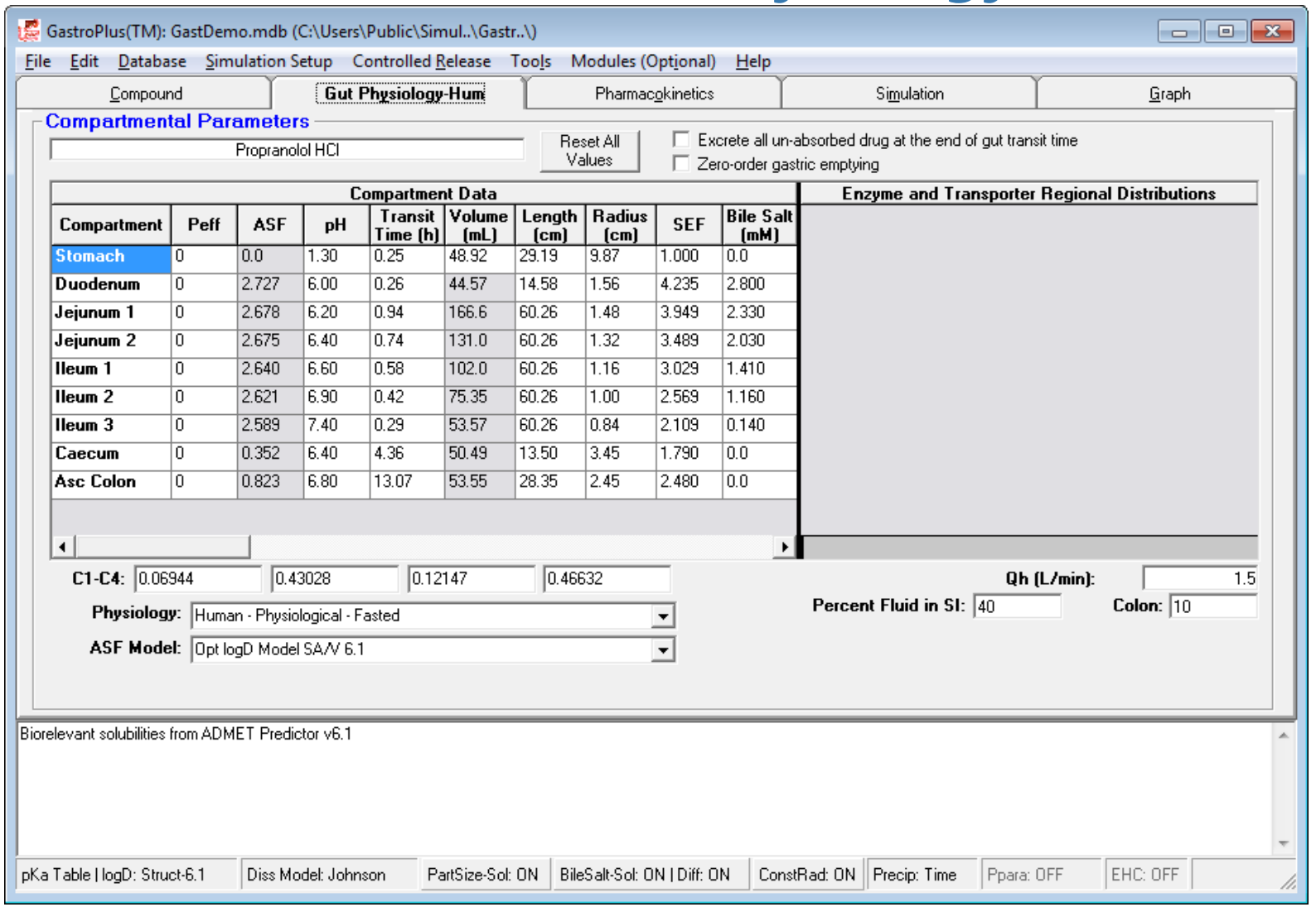
Thank You

Back-up slides

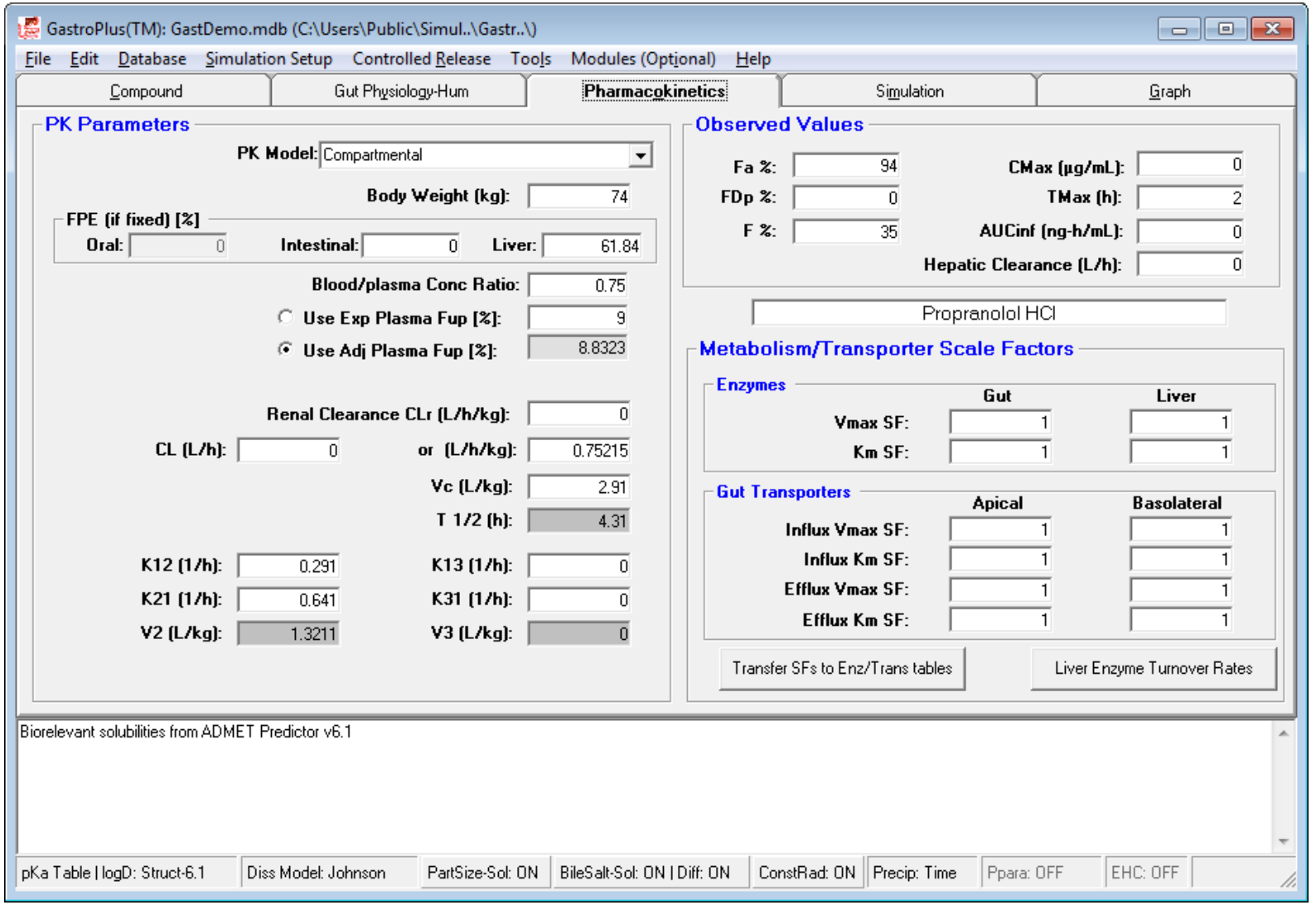
GastroPlus™ user interface: Compound



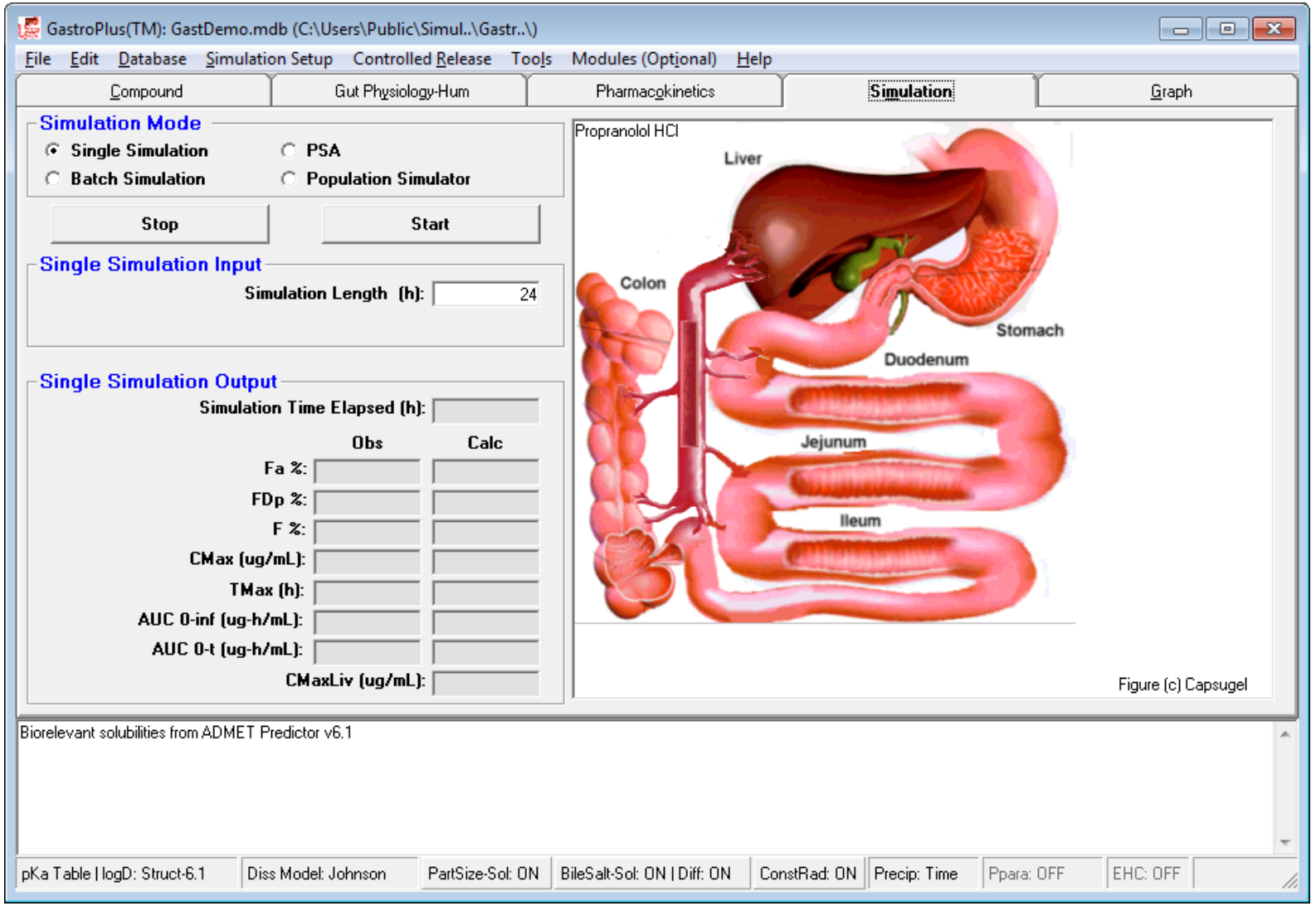
GastroPlus™ user interface: Gut Physiology



GastroPlus™ user interface: Pharmacokinetics



GastroPlus™ user interface: Simulation



GastroPlus™ user interface: Graph