Physiologically Based Biopharmaceutics Modeling and Virtual Bioequivalence Assessment to Support Formulation Development

Joyce Macwan, Ph.D.

Simulations Plus, Inc.

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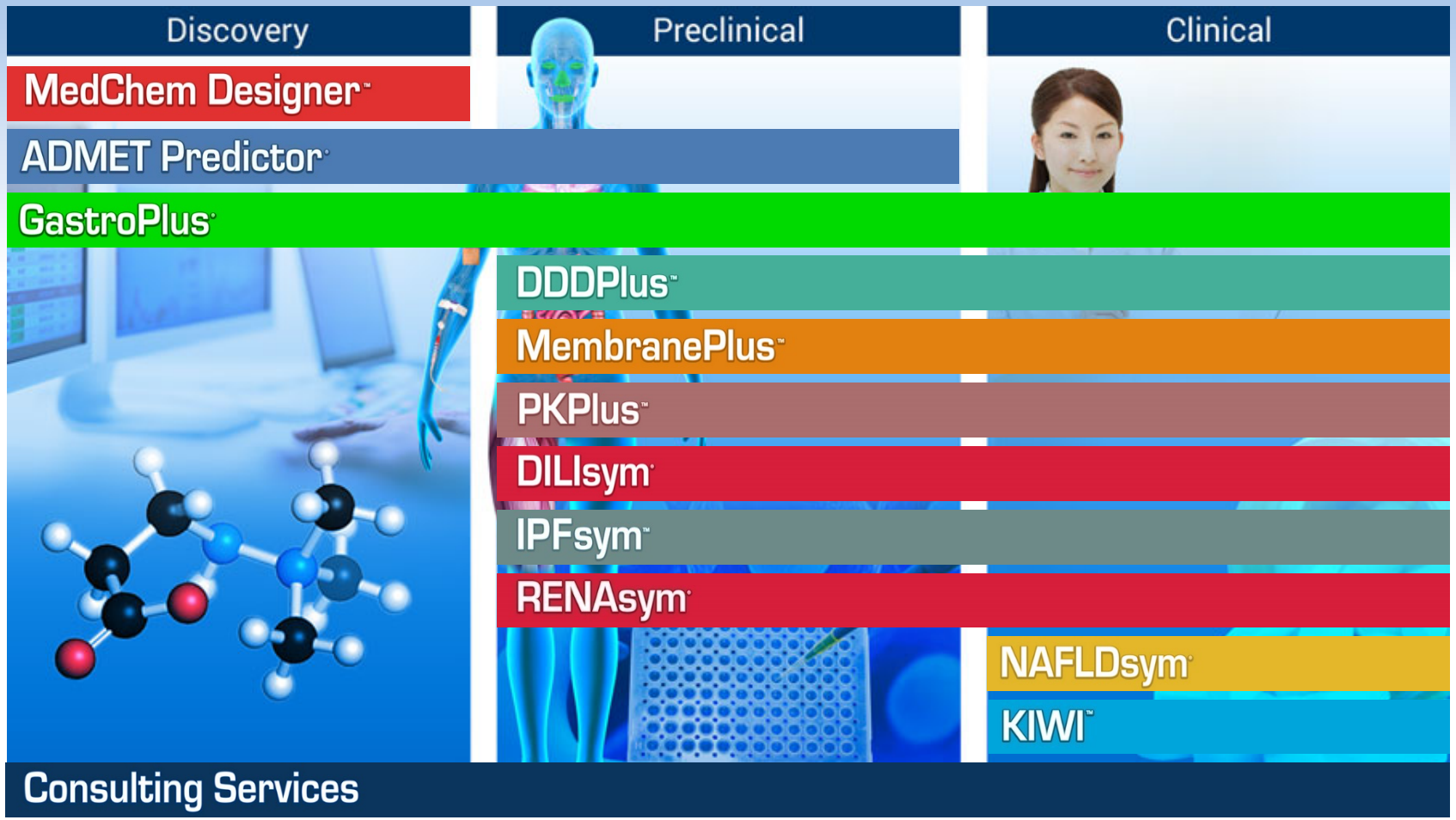
Outline

- **Introduction**
- **Mechanistic Absorption and PK modeling using GastroPlus®**
- **Overview of regulatory submissions**
- **Industrial applications of MAM/PBPK modeling – case studies**
- **Conclusions**

Software and Consulting Solutions from Discovery to Formulation Development



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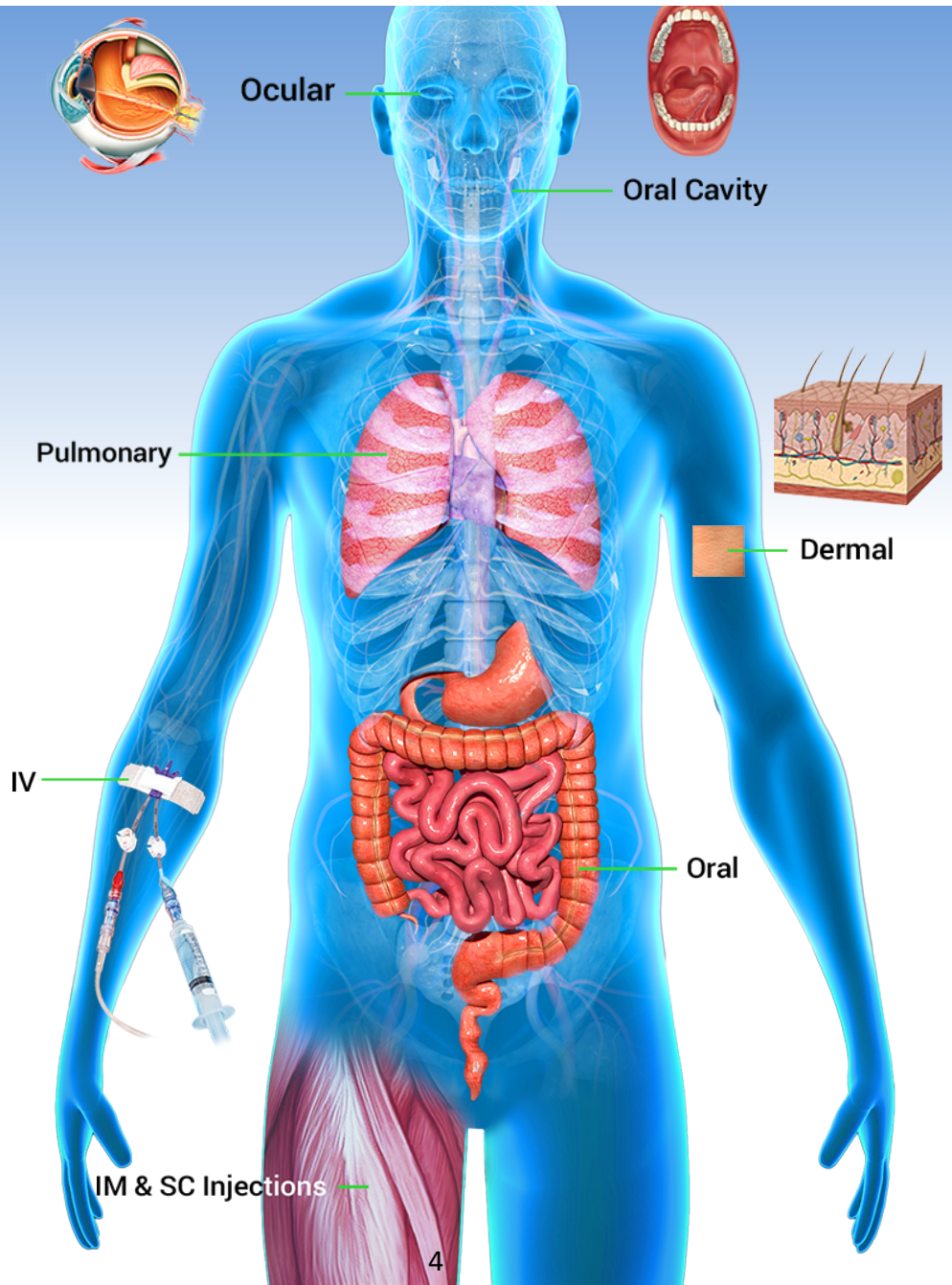
PBBM models defined around the body in GastroPlus®



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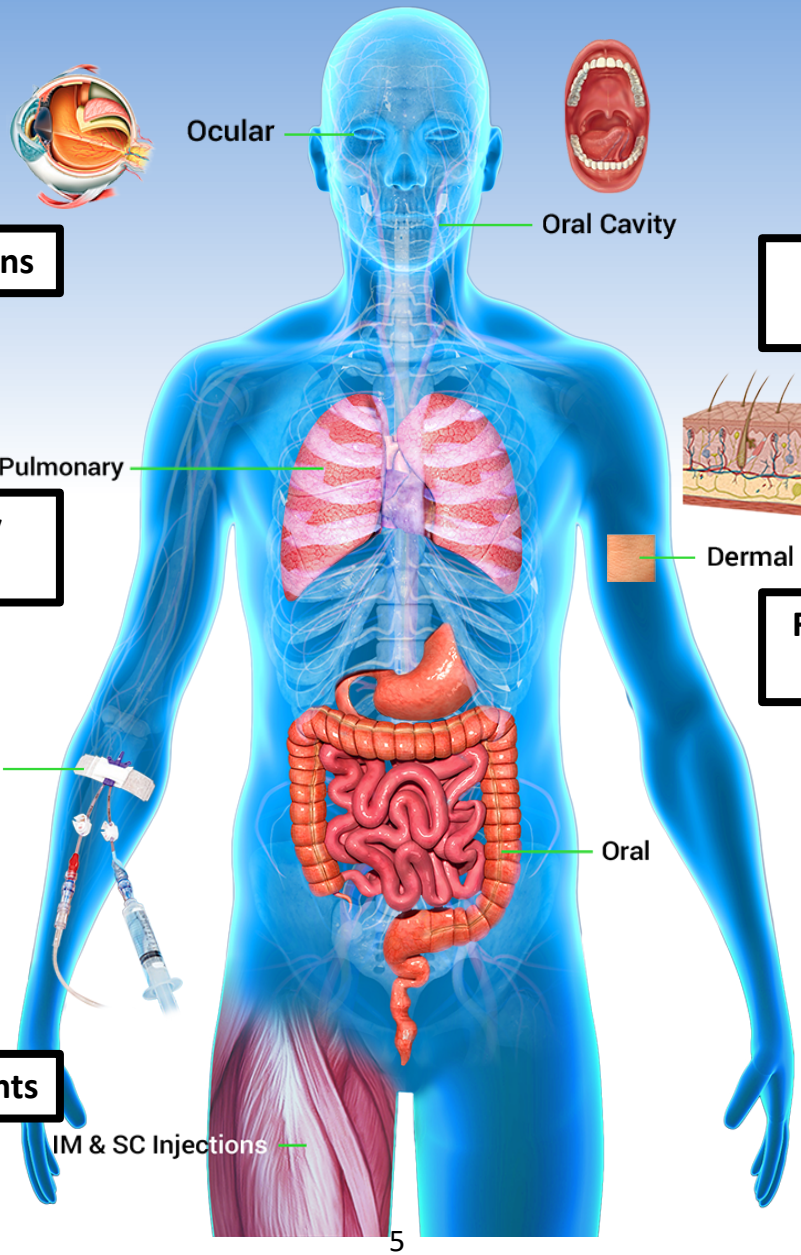
Funded Collaborations



FDA: Ocular model extensions

Cosmetics Europe: Dermal model extensions

Large Pharma: Pulmonary model extensions

FDA: Dermal product critical quality attributes

FDA: LAI model enhancements

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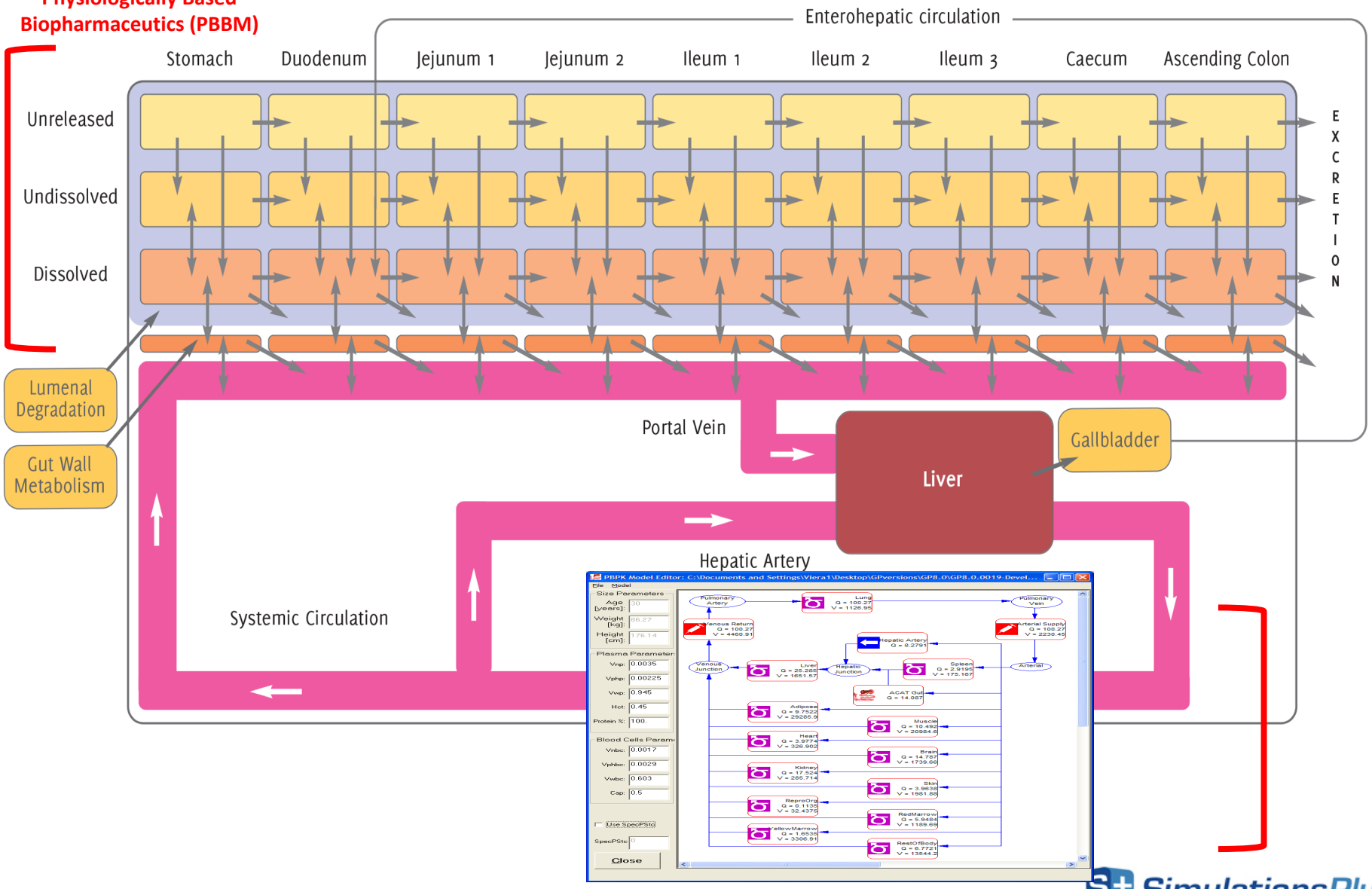
Advanced Compartmental Absorption and Transit Model (ACAT™)

Physiologically Based Biopharmaceutics (PBBM)



Physiologically based Pharmacokinetics (PBPK)

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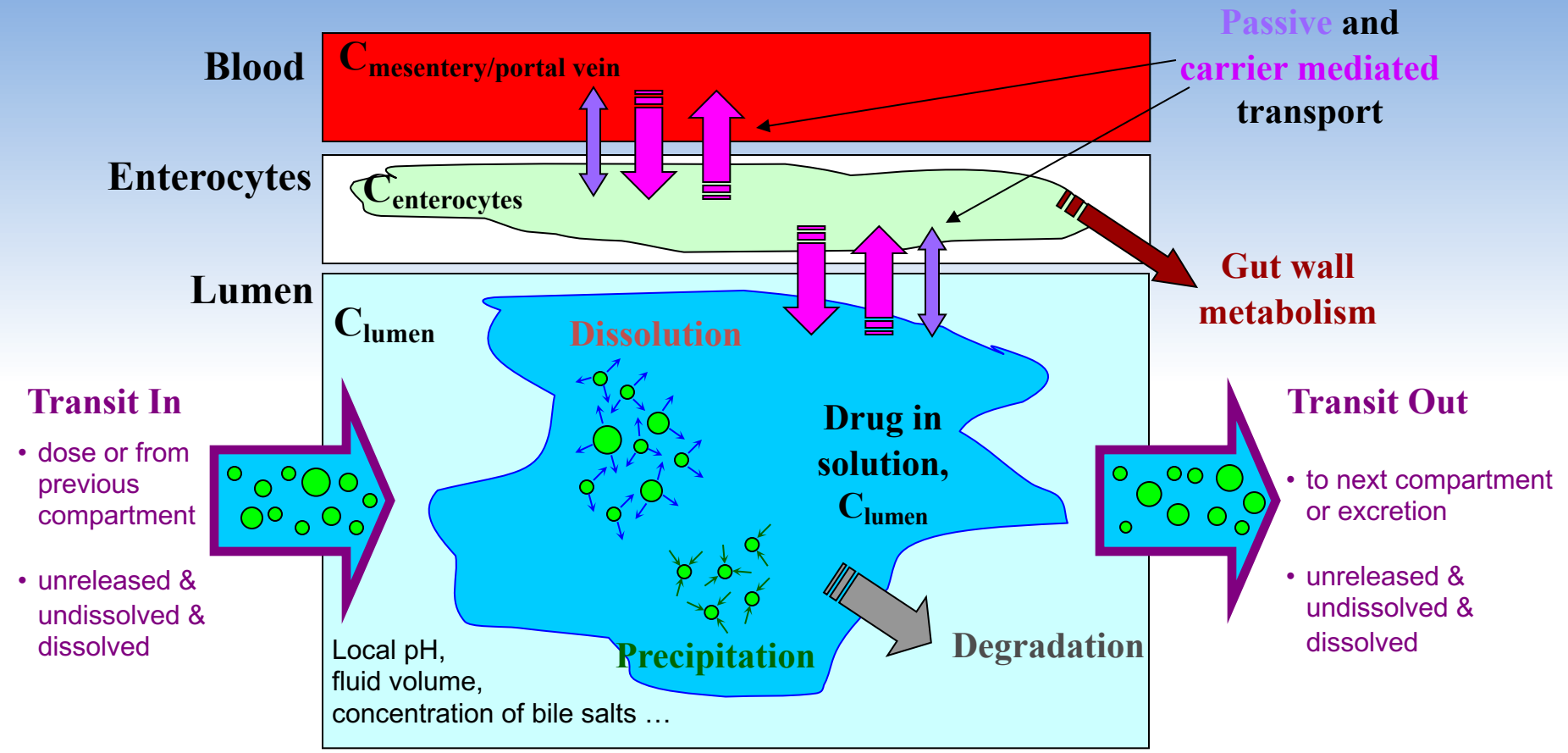
Processes Involved in Oral Absorption



These phenomena:

- **are happening simultaneously**
- **are repeated in each of the compartments of the gastrointestinal tract**

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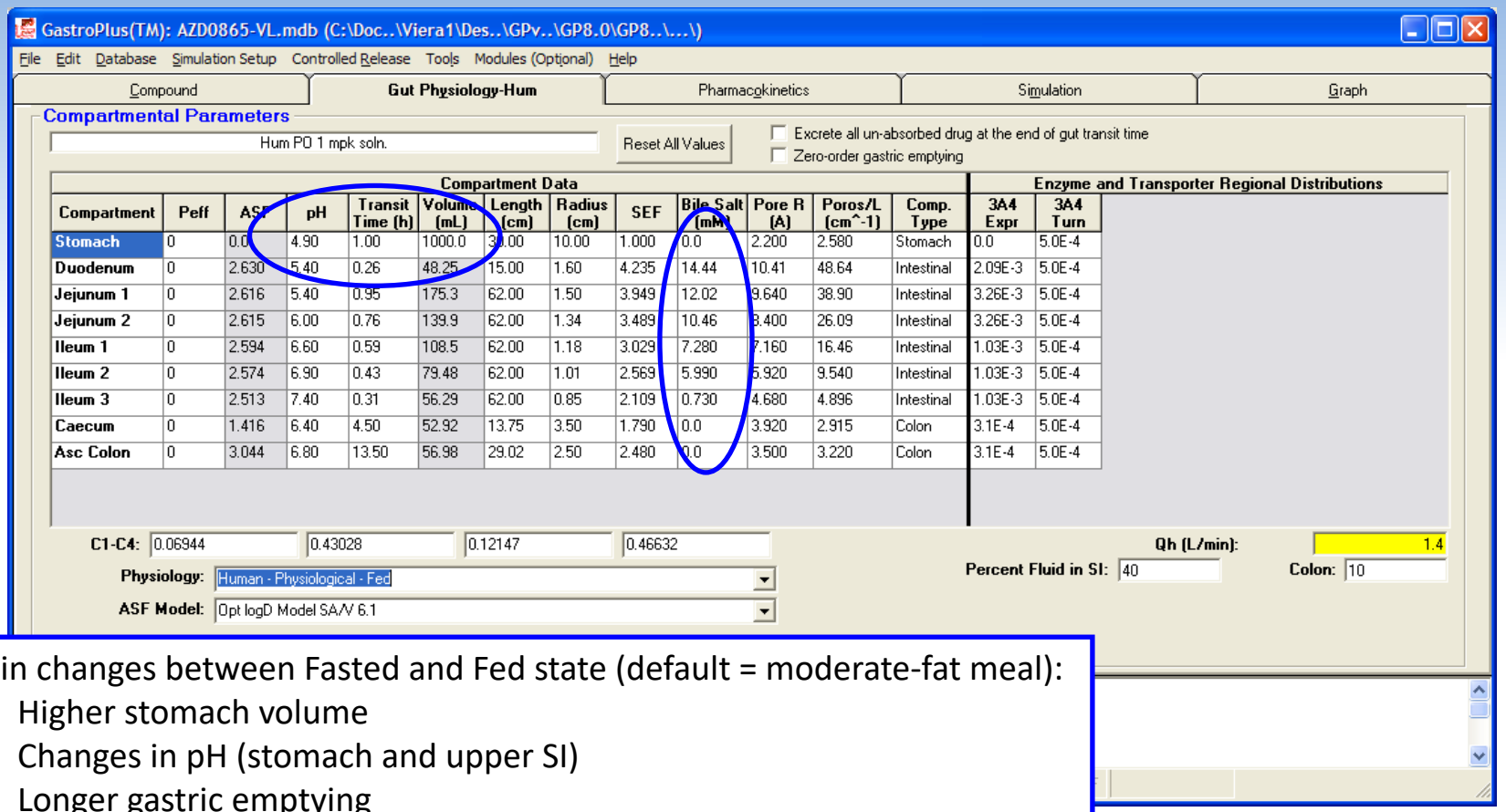
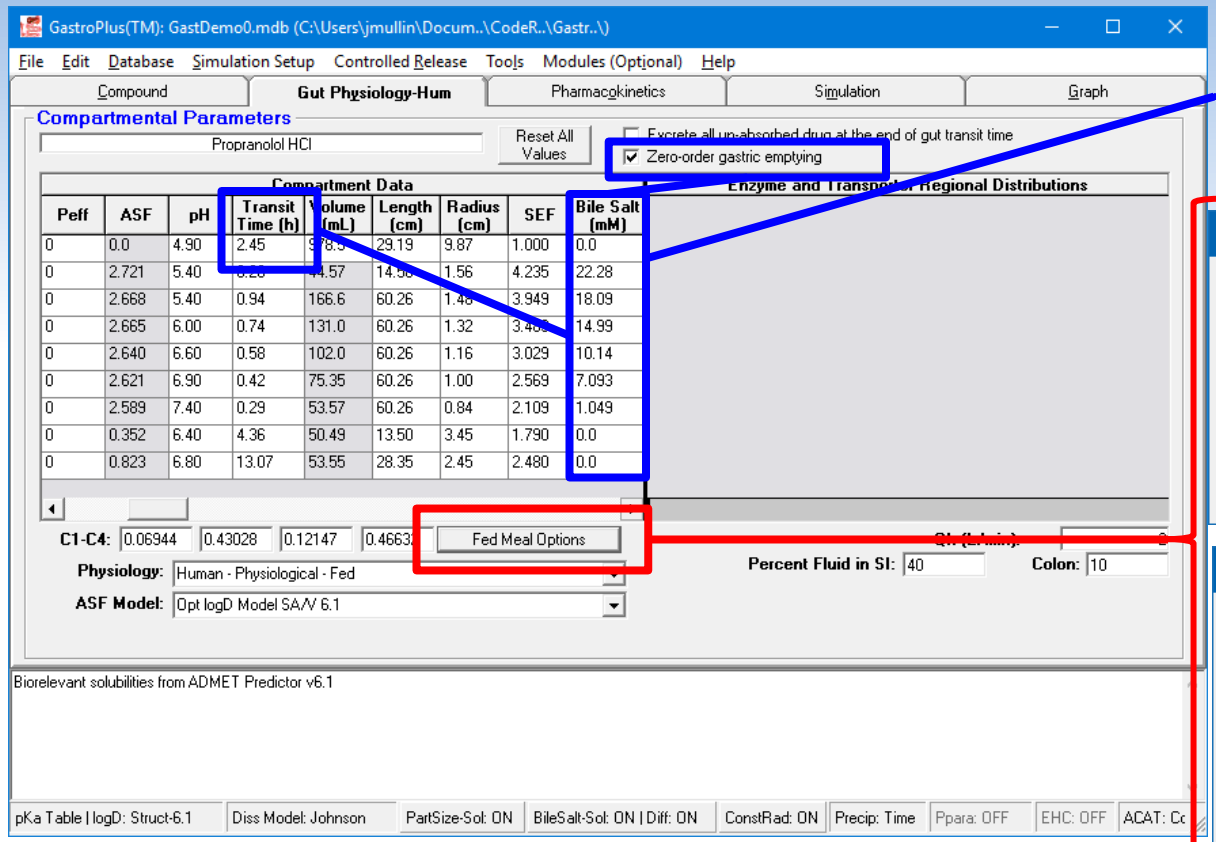
Fed State – ACAT™ Model Changes



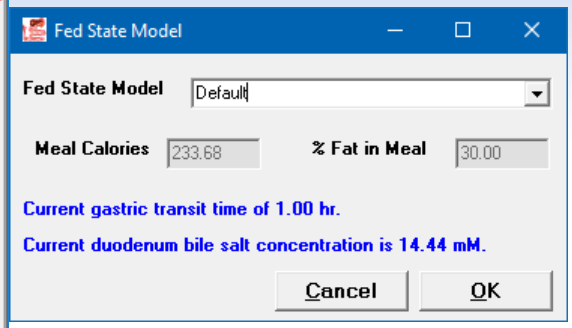
Main changes between Fasted and Fed state (default = moderate-fat meal):

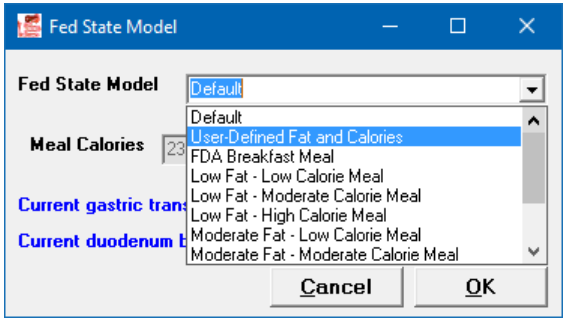
- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations
- Increased liver blood flows

Built-in Fed Physiologies for Different Meal Types



- Link gastric emptying time to meal calories
- Account for effect of fat content on bile salt concentration





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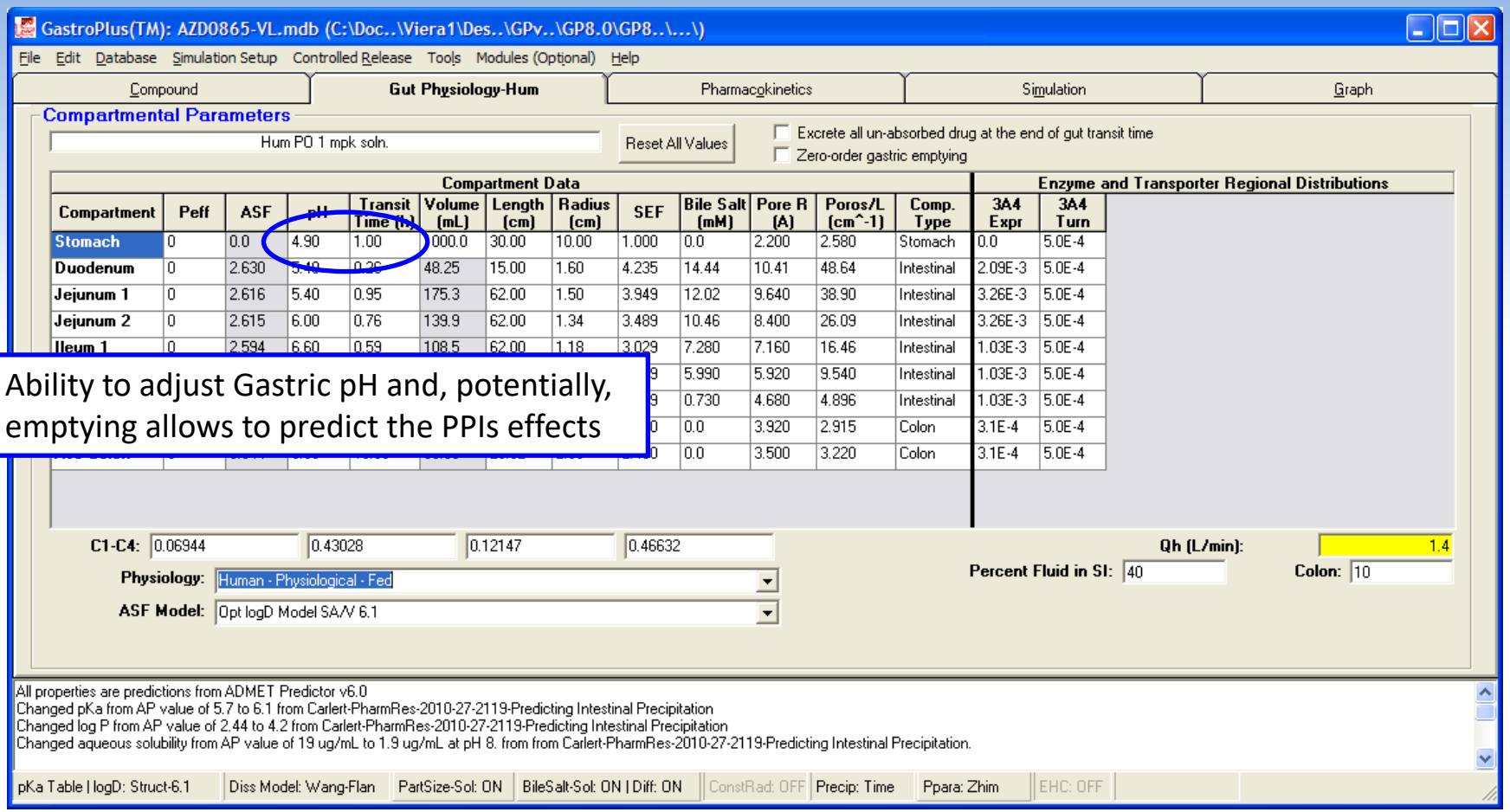
Predicting Proton Pump Inhibitors (PPIs) Effects



Ability to adjust Gastric pH and, potentially, emptying allows to predict the PPIs effects

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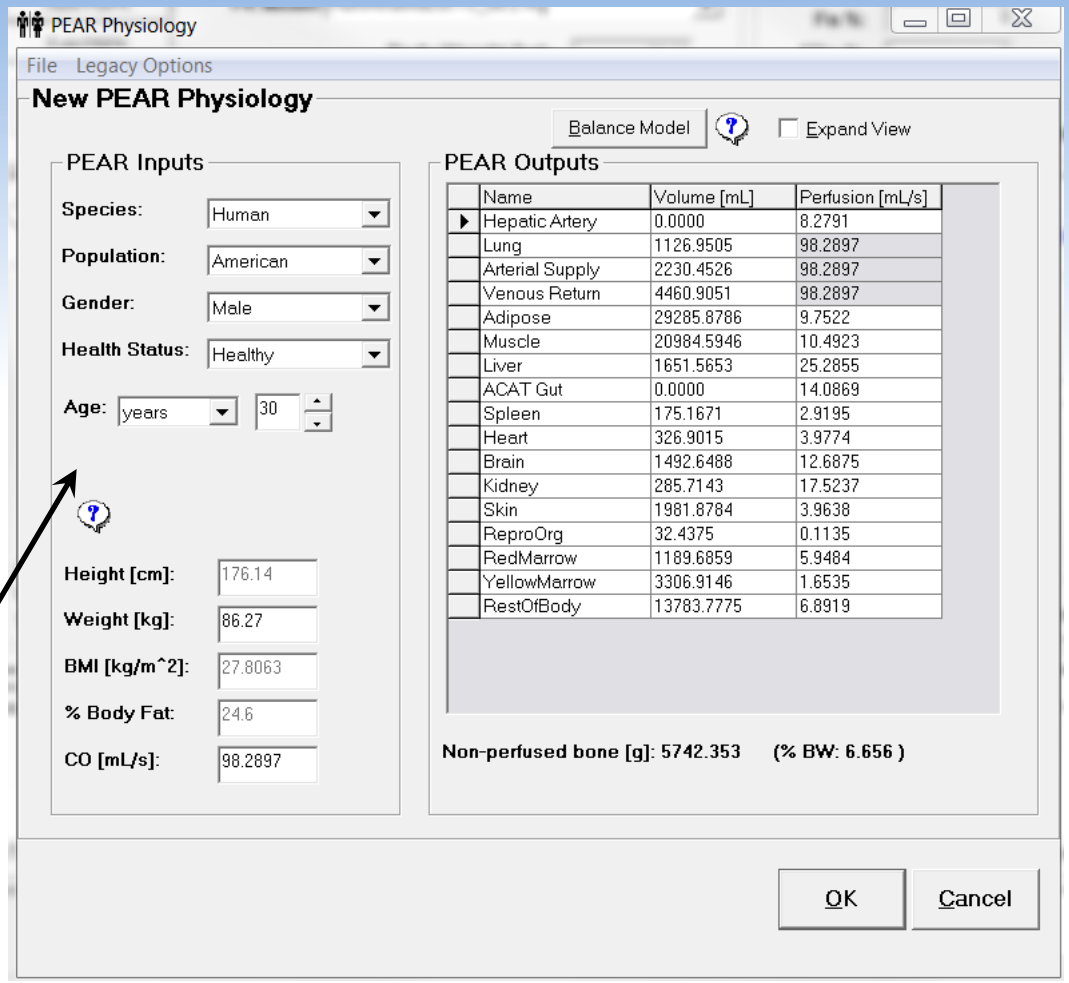
GastroPlus System Physiology Models

1. Select **Species:**
   - **Human**
   - **Rat**
   - **Dog**
   - **Monkey**
   - **Mouse**
   - **Minipig**
   - **Rabbit**

2. For human physiologies, specify **Population, Gender, Health Status** and **Age (pediatrics->adults)**
   - **Population Types:**
     - **American**
     - **Japanese**
     - **Chinese**
   - **Health Status:**
     - **Healthy**
     - **Hepatic Impairment**
     - **Renal Impairment**
     - **Obesity**
     - **Pregnancy**

For infants specify born **at term** or **premature** infant (day 1 of birth, up to 16 weeks premature)



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FDA Workshop (September 2019):
Current State/Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

- **Physiologically based biopharmaceutics modeling (PBBM)**
  - Translate formulation and manufacturing changes into *in vivo* performance
  - Predict impact of variations in critical properties through establishing a 'safe space' via IVIVR/C combined with virtual BE trial simulations
- Today: FDA open to proposals of using PBBM approaches to establish clinically relevant product specifications
  - Proposals should include information about:
    - Modeling approach
    - Scientific justification of the proposed approach
    - Model verification

https://cersi.umd.edu/current-state-and-future-expectations-translational-modeling-strategies-support-drug-product

Common regulatory applications of PBBM in support of drug product quality

Dissolution

- •Bio-predictive ability of dissolution method
- •Clinically relevant dissolution AC/wider AC

Clinically relevant specifications of CMAs and CPPs

- CMAs (e.g., particle size, polymorphic form)
- CPPs (e.g., milling, compression force/hardness process evaluation)

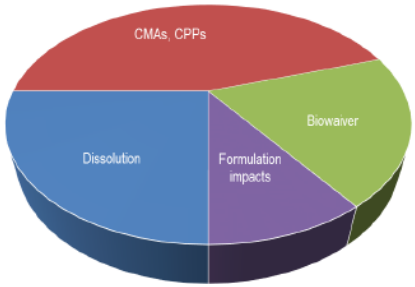
Quality related Bio-waiver

- •Waiver request based on physiologically based IVIVC/IVIVR

Formulation impacts

- Formulation-related food effect
- API form change or formulation change on PPI interactions
- Prediction of product performance by looking at GI local drug concentration and regional absorption

PBBM regulatory submissions in the past decade



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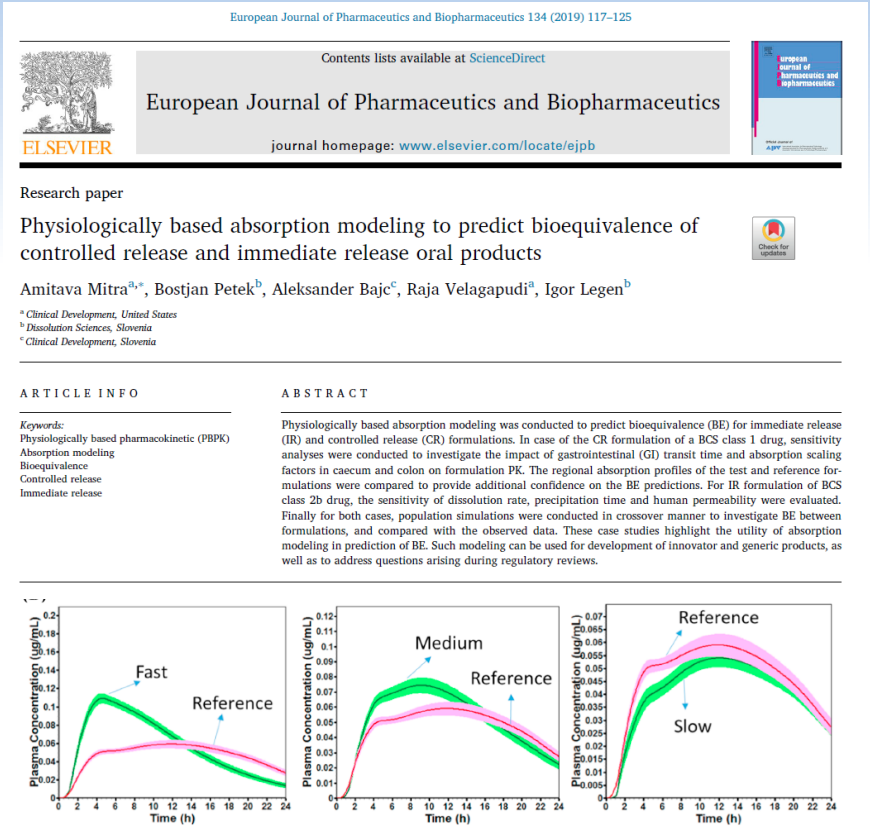
Slide courtesy of L. Zhao (OGD, CDER, FDA; Sept 2019)

Best Practices for Applying PBBM to Assess Virtual Bioequivalence

- Case studies illustrate how PBBM assists with development of innovator and generic products
  - Considerations when using *in vitro* dissolution data to guide formulation simulations
  - Applying virtual BE trial simulations to help define bioequivalence and product specs

Mitra et al. Eur. J. Pharma. Biopharm. 2019



European Journal of Pharmaceutics and Biopharmaceutics 134 (2019) 117–125

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journal homepage: www.elsevier.com/locate/ejpb

Research paper

Physiologically based absorption modeling to predict bioequivalence of controlled release and immediate release oral products

Amitava Mitra[a,*], Bostjan Petek[b], Aleksander Bajc[c], Raja Velagapudi[a], Igor Legen[b]

[a] Clinical Development, United States
[b] Dissolution Sciences, Slovenia
[c] Clinical Development, Slovenia

ARTICLE INFO

Keywords:
Physiologically based pharmacokinetic (PBPK)
Absorption modeling
Bioequivalence
Controlled release
Immediate release

ABSTRACT

Physiologically based absorption modeling was conducted to predict bioequivalence (BE) for immediate release (IR) and controlled release (CR) formulations. In case of the CR formulation of a BCS class 1 drug, sensitivity analyses were conducted to investigate the impact of gastrointestinal (GI) transit time and absorption scaling factors in caecum and colon on formulation PK. The regional absorption profiles of the test and reference formulations were compared to provide additional confidence on the BE predictions. For IR formulation of BCS class 2b drug, the sensitivity of dissolution rate, precipitation time and human permeability were evaluated. Finally for both cases, population simulations were conducted in crossover manner to investigate BE between formulations, and compared with the observed data. These case studies highlight the utility of absorption modeling in prediction of BE. Such modeling can be used for development of innovator and generic products, as well as to address questions arising during regulatory reviews.

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PBBM Simulations and Virtual BE to Justify Product Specifications

- Case studies illustrate how PBBM IVIVRs and virtual BE trial simulations support product specs
  - Recommendations when traditional IVIVCs cannot be developed due to lack of data
  - Applying virtual BE trial simulations to help define bioequivalence and product specs

AAPS PharmSciTech (2020) 21: 18
DOI: 10.1208/s12249-019-1566-x

Check for updates

Research Article

In vitro–In vivo Relationship and Bioequivalence Prediction for Modified-Release Capsules Based on a PBPK Absorption Model

Rebeka Jereb,[1,3] Jerneja Opara,[2] Igor Legen,[2] Boštjan Petek,[2] and Darja Grabnar-Peklar[2]

Received 12 June 2019; accepted 9 October 2019; published online 9 December 2019

Abstract. A physiologically based pharmacokinetic (PBPK) absorption model was developed in GastroPlus™ based on data on intravenous, immediate-release (IR), and modified-release (MR) drug products. The predictability of the model was evaluated by comparing predicted and observed plasma concentration profiles; average prediction errors (PE) were below 10%. IVIVR was developed using mechanistic deconvolution for a MR drug product to evaluate the *in vivo* effect of a proposed change in dissolution specification. The predictability of the IVIVR was evaluated and PE were below 10%; however, external validation was not possible due to the lack of data. The developed PBPK absorption model and IVIVR were used to predict plasma concentration profiles and pharmacokinetic (PK) parameters for a hypothetical formulation with 0% of drug dissolved in 2 h in *in vitro* dissolution test. Both methods predicted the insignificant effect of a change in *in vitro* dissolution profile on *in vivo* product performance. The bioequivalence of a hypothetical formulation to the test product was evaluated using virtual clinical trial. The performed analysis supported the proposed change in dissolution specification. A validated PBPK

Jereb et al. AAPS PharmSciTech 2020

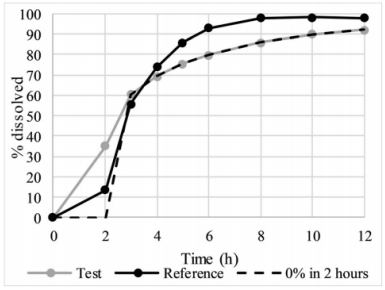


Fig. 1. Dissolution profiles of test and reference MR capsules in 500 ml 0.003% polysorbate 80 for 2 h followed by 500 mL phosphate buffer pH 7.2 for 10 h at 37°C, Apparatus 2, USP, 100 rpm with sinker. A hypothetical dissolution profile with 0% of drug dissolved in 2 h is also presented

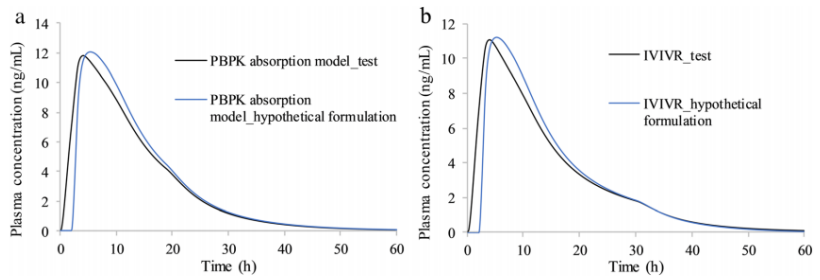
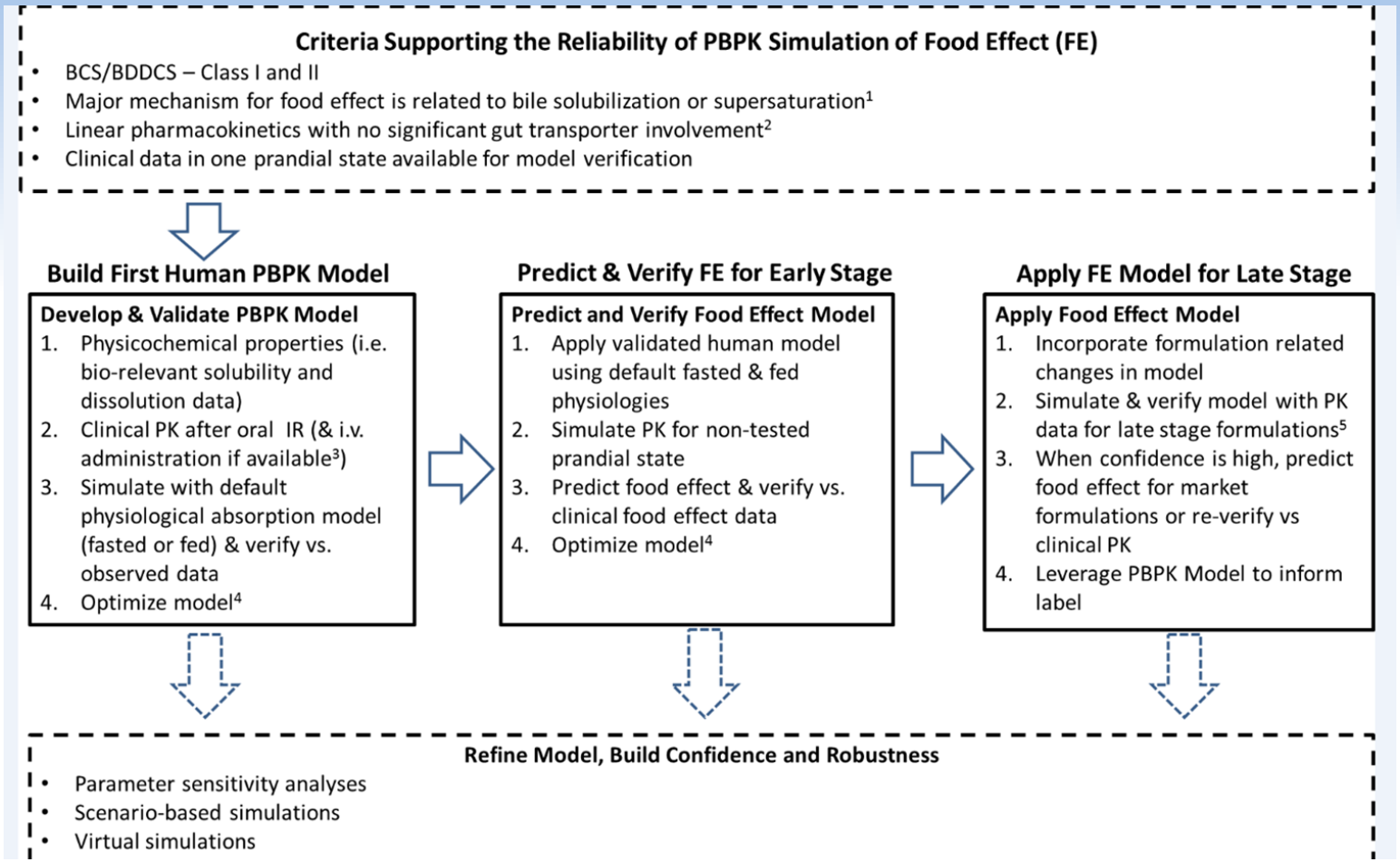


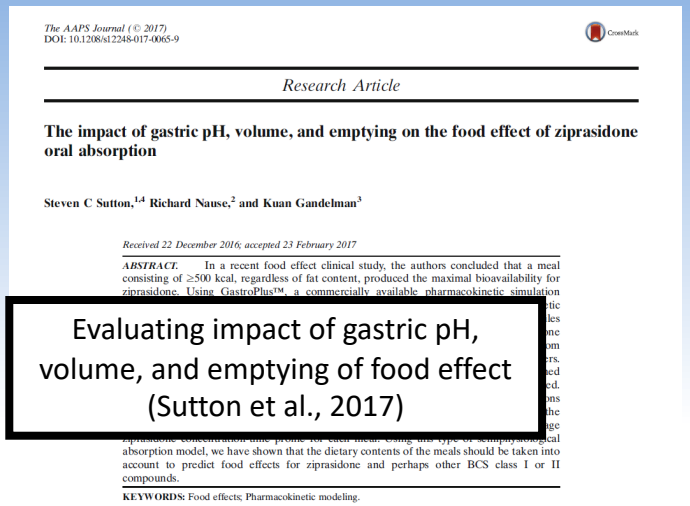
Fig. 5. Predicted mean plasma concentration profiles of a test MR formulation and a hypothetical formulation with 0% of drug dissolved in 2 h *in vitro* using **a** PBPK absorption model or **b** IVIVR equation and appropriate dissolution profiles

Food Effect Projections via Physiologically Based Pharmacokinetic Modeling: Predictive Case Studies



Heimbach and Parrott. GastroPlus User Group Webinar – June 2018
Tistaert et al. J. Pharm. Sci. (2018) Jun 12

Food Effect Predictions – Select References



The AAPS Journal (© 2017)
DOI: 10.1208/s12248-017-0065-9

Research Article

The impact of gastric pH, volume, and emptying on the food effect of ziprasidone oral absorption

Steven C Sutton,[1,4] Richard Nause,[2] and Kuan Gandelman[3]

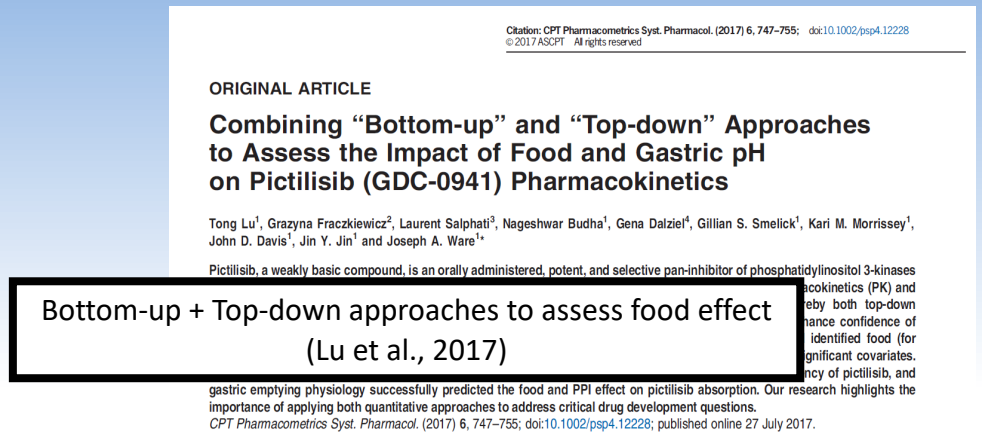
Received 22 December 2016; accepted 23 February 2017

ABSTRACT. In a recent food effect clinical study, the authors concluded that a meal consisting of ≥500 kcal, regardless of fat content, produced the maximal bioavailability for ziprasidone. Using GastroPlus™, a commercially available pharmacokinetic simulation

absorption model, we have shown that the dietary contents of the meals should be taken into account to predict food effects for ziprasidone and perhaps other BCS class I or II compounds.

KEYWORDS: Food effects; Pharmacokinetic modeling.

Evaluating impact of gastric pH, volume, and emptying of food effect (Sutton et al., 2017)



Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 747–755; doi:10.1002/psp4.12228
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ORIGINAL ARTICLE

Combining "Bottom-up" and "Top-down" Approaches to Assess the Impact of Food and Gastric pH on Pictilisib (GDC-0941) Pharmacokinetics

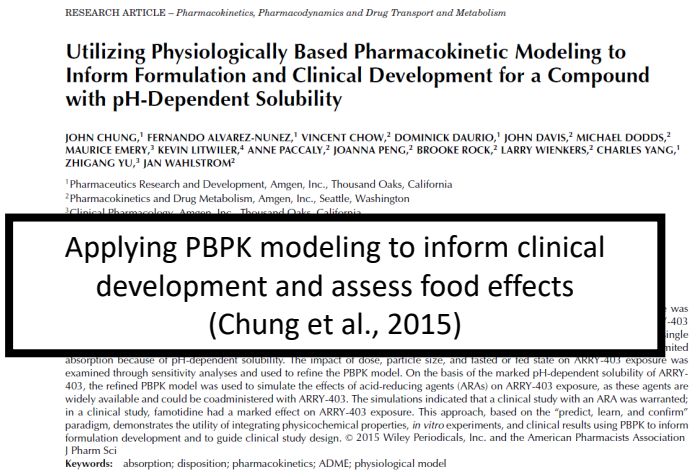
Tong Lu[1], Grazyna Fraczkiewicz[2], Laurent Salphati[3], Nageshwar Budha[1], Gena Dalziel[4], Gillian S. Smelick[1], Kari M. Morrissey[1], John D. Davis[1], Jin Y. Jin[1] and Joseph A. Ware[1]*

Pictilisib, a weakly basic compound, is an orally administered, potent, and selective pan-inhibitor of phosphatidylinositol 3-kinases

gastric emptying physiology successfully predicted the food and PPI effect on pictilisib absorption. Our research highlights the importance of applying both quantitative approaches to address critical drug development questions.

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 747–755; doi:10.1002/psp4.12228; published online 27 July 2017.

Bottom-up + Top-down approaches to assess food effect (Lu et al., 2017)



RESEARCH ARTICLE – *Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism*

Utilizing Physiologically Based Pharmacokinetic Modeling to Inform Formulation and Clinical Development for a Compound with pH-Dependent Solubility

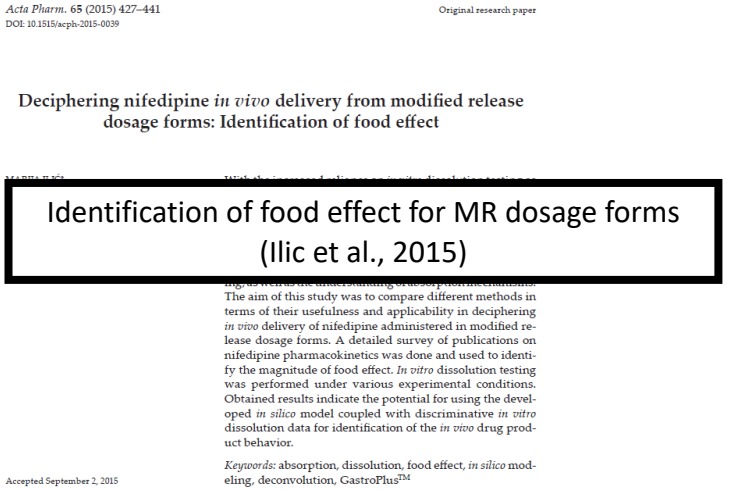
JOHN CHUNG,[1] FERNANDO ALVAREZ-NUNEZ,[1] VINCENT CHOW,[2] DOMINICK DAURIO,[1] JOHN DAVIS,[2] MICHAEL DODDS,[2] MAURICE EMERY,[3] KEVIN LITWILER,[4] ANNE PACCALY,[2] JOANNA PENG,[2] BROOKE ROCK,[2] LARRY WIENKERS,[2] CHARLES YANG,[1] ZHIGANG YU,[3] JAN WAHLSTROM[2]

[1]Pharmaceutics Research and Development, Amgen, Inc., Thousand Oaks, California
[2]Pharmacokinetics and Drug Metabolism, Amgen, Inc., Seattle, Washington

absorption because of pH-dependent solubility. The impact of dose, particle size, and fasted or fed state on ARRY-403 exposure was examined through sensitivity analyses and used to refine the PBPK model. On the basis of the marked pH-dependent solubility of ARRY-403, the refined PBPK model was used to simulate the effects of acid-reducing agents (ARAs) on ARRY-403 exposure, as these agents are widely available and could be coadministered with ARRY-403. The simulations indicated that a clinical study with an ARA was warranted; in a clinical study, famotidine had a marked effect on ARRY-403 exposure. This approach, based on the "predict, learn, and confirm" paradigm, demonstrates the utility of integrating physicochemical properties, *in vitro* experiments, and clinical results using PBPK to inform formulation development and to guide clinical study design. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: absorption; disposition; pharmacokinetics; ADME; physiological model

Applying PBPK modeling to inform clinical development and assess food effects (Chung et al., 2015)



Acta Pharm. 65 (2015) 427–441
DOI: 10.1515/acph-2015-0039

Original research paper

Deciphering nifedipine *in vivo* delivery from modified release dosage forms: Identification of food effect

The aim of this study was to compare different methods in terms of their usefulness and applicability in deciphering *in vivo* delivery of nifedipine administered in modified release dosage forms. A detailed survey of publications on nifedipine pharmacokinetics was done and used to identify the magnitude of food effect. *In vitro* dissolution testing was performed under various experimental conditions. Obtained results indicate the potential for using the developed *in silico* model coupled with discriminative *in vitro* dissolution data for identification of the *in vivo* drug product behavior.

Keywords: absorption, dissolution, food effect, *in silico* modeling, deconvolution, GastroPlus™

Accepted September 2, 2015

Identification of food effect for MR dosage forms (Ilic et al., 2015)

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Approved drug product applications supported by GastroPlus® simulations

Recent Approved Drug Product Applications

- ALECENSA® (**absorption/PPI DDI** informing drug labeling)
- BRAFTOVI® (**metabolism DDI** accepted by regulatory agencies)
- CALQUENCE® (**particle size specs** accepted by regulatory agencies)
- FARYDAK® (**food effect/PPI predictions** informing drug labeling)
- INLYTA® (**transporter DDI** accepted by regulatory agencies)
- KISQALI® (**gastric pH predictions** accepted by regulatory agencies)
- MEKINIST® (**transporter DDI** accepted by regulatory agencies)
- MEKTOVI® (**metabolism DDI** accepted by regulatory agencies)
- OPSUMIT® (**particle size specs** accepted by regulatory agencies)
- TAMIFLU® (**pediatric** PBPK predictions informing **dose selection**)
- ZURAMPIC® (**wider product specs** accepted by regulatory agencies)
- … and more!

<u>No other PBBM/PBPK platform has the diversity in applications!</u>

Rates of Acceptance of PBPK Analysis by FDA/EMA

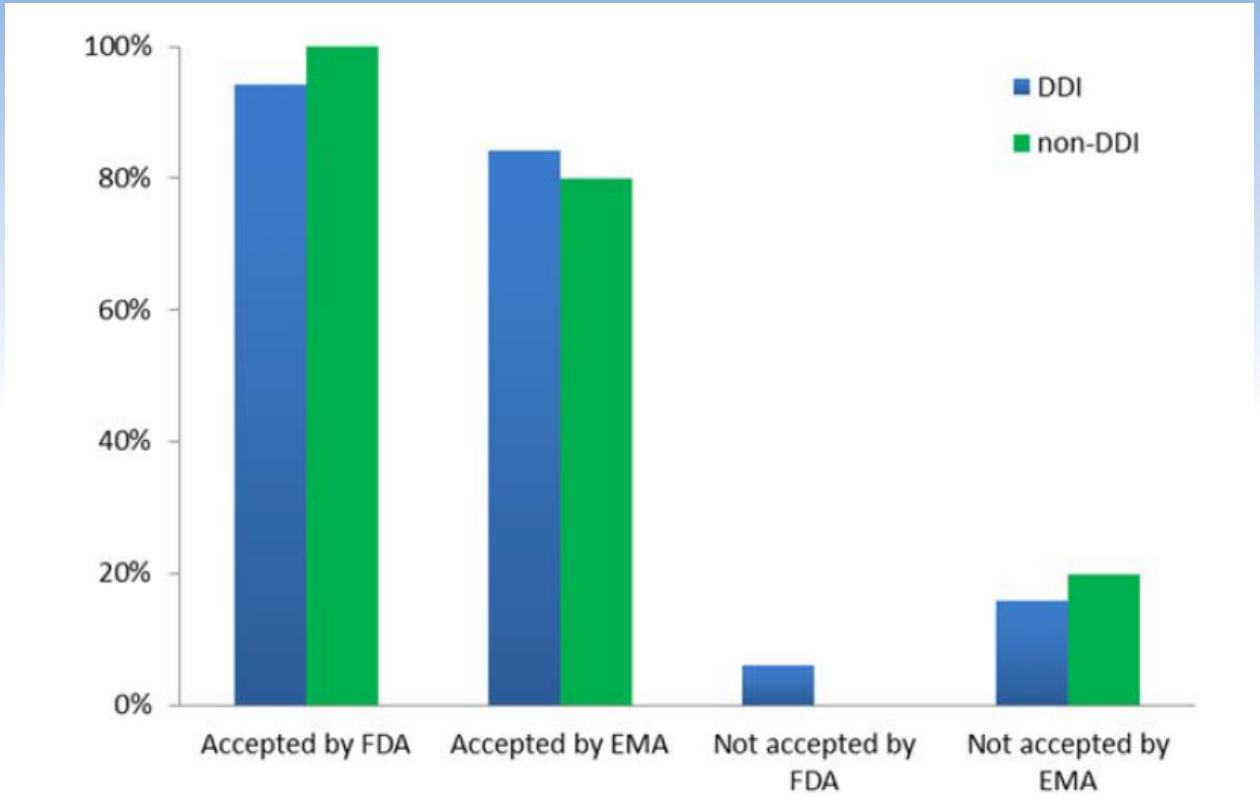

Figure 3 Rates of acceptance of PBPK analyses by the FDA or EMA among DDI and non-DDI related submissions.

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 104 NUMBER 1 | JULY 2018; doi:10.1002/cpt.1013

PBPK Modeling Impact for Regulatory Activities in the FDA OGD (Calendar Year 2016)

Type	No.	Examples
ANDA Reviews	20	❖ PD modeling and simulation for Methylphenidate ER product and asthma controllers
CP, CC, Pre-ANDA meetings	54	❖ Development of BE criteria for pain killers ❖ Assessment of BE standards for GI locally acting products ❖ Simulation of in vivo alcohol dose dumping studies
BE Guidances	33	❖ Simulations for the development of BE criteria for HVDs and NTI drugs
Regulatory Research Study	37	❖ PK/PD modeling and simulation to determine the appropriate study design and evaluate BE between generic anti-epilepsy drugs and immunosuppressant drugs in patients

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ANDA: abbreviated new drug application; BE: bioequivalence: CP: citizen petition; CC: controlled correspondence; GI: gastrointestinal; HVD: highly variable drugs; NTI: narrow therapeutic index.

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

Highlights of PBPK Impacts (2016) at the FDA Office of Generic Drugs

Category	Example Drug	Impact on regulatory decision making
Dissolution	Fingolimod, Oxybutynin	Risk assessment for not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths
Product quality	Prasugrel	Conclusion that less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including subjects on PPI
Mechanism change risks	Venlafaxine	Model predicted that a delayed onset of venlafaxine release up to 4 h predicted to demonstrate BE for the openable matrix release mechanism against the osmotic pump based release mechanism
PPI effect	Several ER products	Risk assessment of changing drug release to a PH dependent mechanism
PK metrics determination	Mesalamine Suppositories	Determination of PK metrics for BE evaluation
Alcohol dose dumping	Metformin Hydrochloride ER Tablet	Assessment of alcohol dose dumping potential
Virtual simulation	Methylphenidate	Assessment of using PBPK model in combination with a two way crossover study to meet the guidance recommendation of a four way crossover study for BE assessment

PPI: proton pump inhibitor
ER: extended release

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

Selected FDA Publications

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

...24474

...idely used for the treatment of attention deficit ...AMP salts ER capsules and dextroamphetamine ... surveillance and bioequivalence (BE) guidance ...re conducted to assess BE in various populations ...al. The models were also used to predict phar- ...pecification after the development of *in vitro–in* ...metrics to the changes in formulation variables.

Published 2015. This article is a U.S. Government work and is in the public domain in the USA J Pharm Sci

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

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

Abstract. To implement Quality by Design (QbD) in drug development, scientists need tools that link drug products 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 factor... valida... explor... used t... critica... for th... decre... Virtua... test m... predic...

KEY WORDS: advanced compartmental absorption and transit (ACAT) model; gastroplus™; modified 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. Bykadi • Christopher D. Ellison • Yongheng Yang • Barbara M. Davit • Mansoor A. Khan

Received: 28 February 2012 / Accepted: 9 August 2012

ABSTRACT

Purpose To determine if an IVIVC model can predict PK profiles of varying formulations of a BCS Class I drug that is a salt of a weak base.

Method An IVIVC model (Level A) was created by correlating 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 five test products that varied in formulation characteristics.

Results The model passed internal validation for predicted Cmax 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
IVIVC	*in vitro–in vivo* correlation
k_e	constant of elimination
MAPE	mean absolute percentage error
rpm	revolutions per minute
SUPAC-MR	scale up post approval changes modified release
V_d	volume of distribution
$\%PE_{AUC}$	percent error of AUC prediction
$\%PE_{Cmax}$	percent error of C_{max} prediction

INTRODUCTION

In vitro–in vivo correlation (IVIVC) 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 IVIVC 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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Published online: 22 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 Dr...

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

Virtual BE trial simulations for warfarin

(Zhang et al., 2017)

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Case Study:
Crossover Trials to Show BE after Manufacturing Changes

M&S Objectives

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

- With GastroPlus, could they apply for 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?

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

Proposed Modeling Tasks

- Part I: determine the most appropriate absorption/PBPK model for the API across several doses for the non-engineered lots
- Part II: assess the effect of particle size on API exposure for the immediate release formulation
- Part III: evaluate predicted bioequivalence of the tablets manufactured with particle-engineered (PE) API (narrower particle size distribution) versus the tablets manufactured with non particle-engineered (NPE) API (broader particle size distribution)

Part I: Building the Baseline Model: Key Modeling Parameters

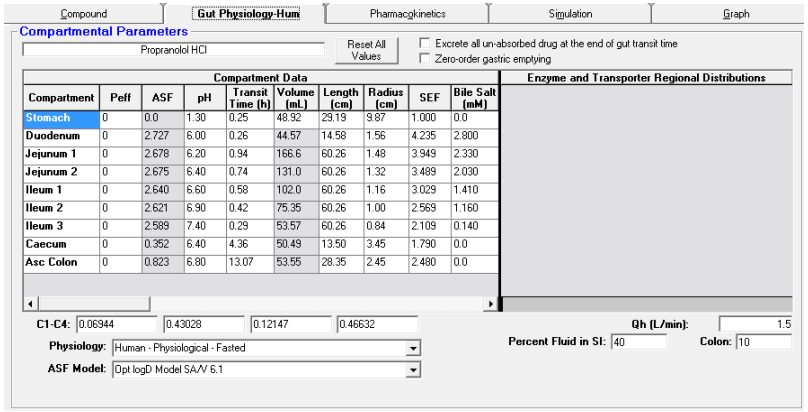
- **Canagliflozin -** BCS Class IV drug
- Neutral compound
- Aqueous solubility = 10 µg/mL
- Significant solubilization by bile salts
- Intermediate lipophilicity
- No food effect

Various Particle Size Used in Clinical Studies

NPE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)
NPE Lot 1	20	63	173
NPE Lot 2	8	179	512
NPE Lot 3	15	49	142
NPE Lot 4	31	86	348
NPE Lot 5	26	78	276
NPE Lot 6	9	29	101
NPE Lot 7	11	35	114
NPE Lot 8	12	37	124
NPE Lot 9	10	36	119
NPE Lot 10	13	45	138
NPE Lot 11	11	35	99

PE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)
PE Lot 1	16	40	88
PE Lot 2	20	49	102
PE Lot 3	22	53	108
PE Lot 4	19	39	71
PE Lot 5	17	35	67
PE Lot 6	23	48	93
PE Lot 7	21	44	87
PE Lot 8	21	45	90
PE Lot 9	24	50	94
PE Lot 10	21	45	89
PE Lot 11	19	42	88
PE Lot 12	22	47	95

API: active pharmaceutical ingredient; d10, d50, and d90: diameter for which 10%, 50%, and 90% (respectively) by volume of the particles are less than this value; NPE: non-particle-engineered; PE: particle-engineered



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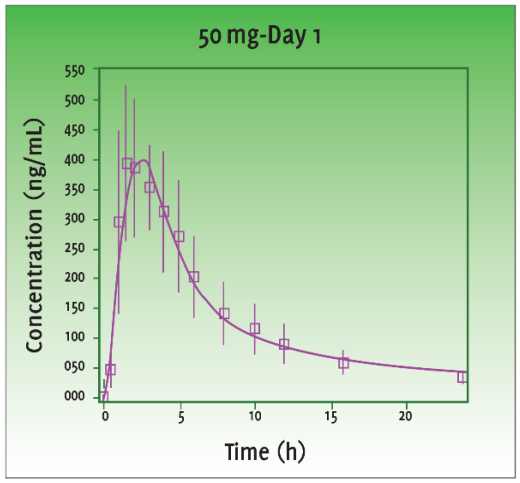
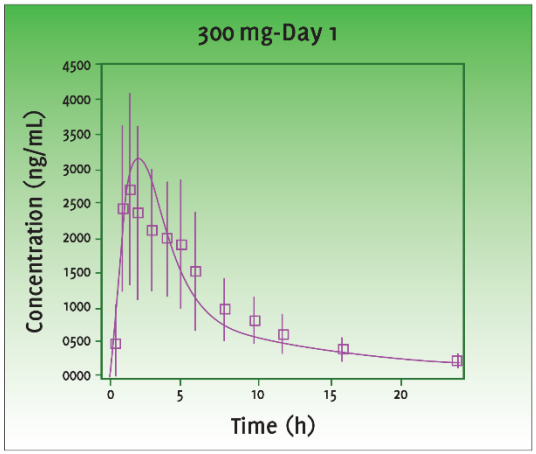
Part I: Simulation Results for Baseline Models of Non-Engineered Lots



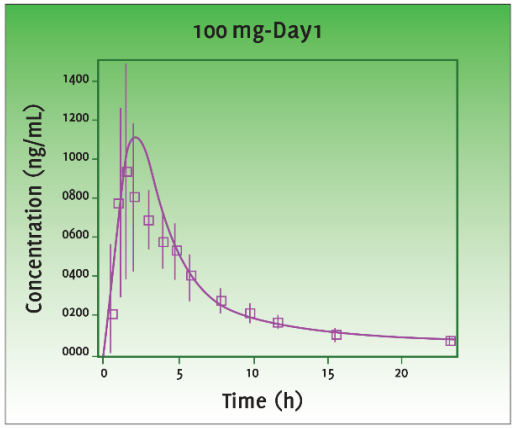
Total simulation time (h): 24

Result	Observ	Simul
Fa (%)_____	0	85.907
FD_p (%) _____	0	85.907
F (%)o_____	0	71.303
Cmax (ng/mL):__	391.2	399.12
Tmax (h): _____	1.5	2.56
AUC o-inf (ng-h/mL)	3563.7	3739.6
AUC o-t (ng-h/mL):_	3139.1	3702
Cmax Liver (ng/mL): _____		531.85



Total simulation time (h): 24

Result	Observ	Simul
Fa (%)_____	0	96.422
FD_p (%) _____	0	96.422
F (%)o_____	0	80.03
Cmax (ng/mL):__	2768	3245.8
Tmax (h): _____	1.5	2.08
AUC o-inf (ng-h/mL)	26290	24970
AUC o-t (ng-h/mL):_	22590	20990
Cmax Liver (ng/mL): _____		4079.7



Total simulation time (h): 24

Result	Observ	Simul
Fa (%)_____	0	85.907
FD_p (%) _____	0	85.907
F (%)o_____	0	71.303
Cmax (ng/mL):__	926.3	399.12
Tmax (h): _____	1.5	2.56
AUC o-inf (ng-h/mL)	7545.6	8462.2
AUC o-t (ng-h/mL):_	6358.8	7117.3
Cmax Liver (ng/mL): _____		1385.9

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.

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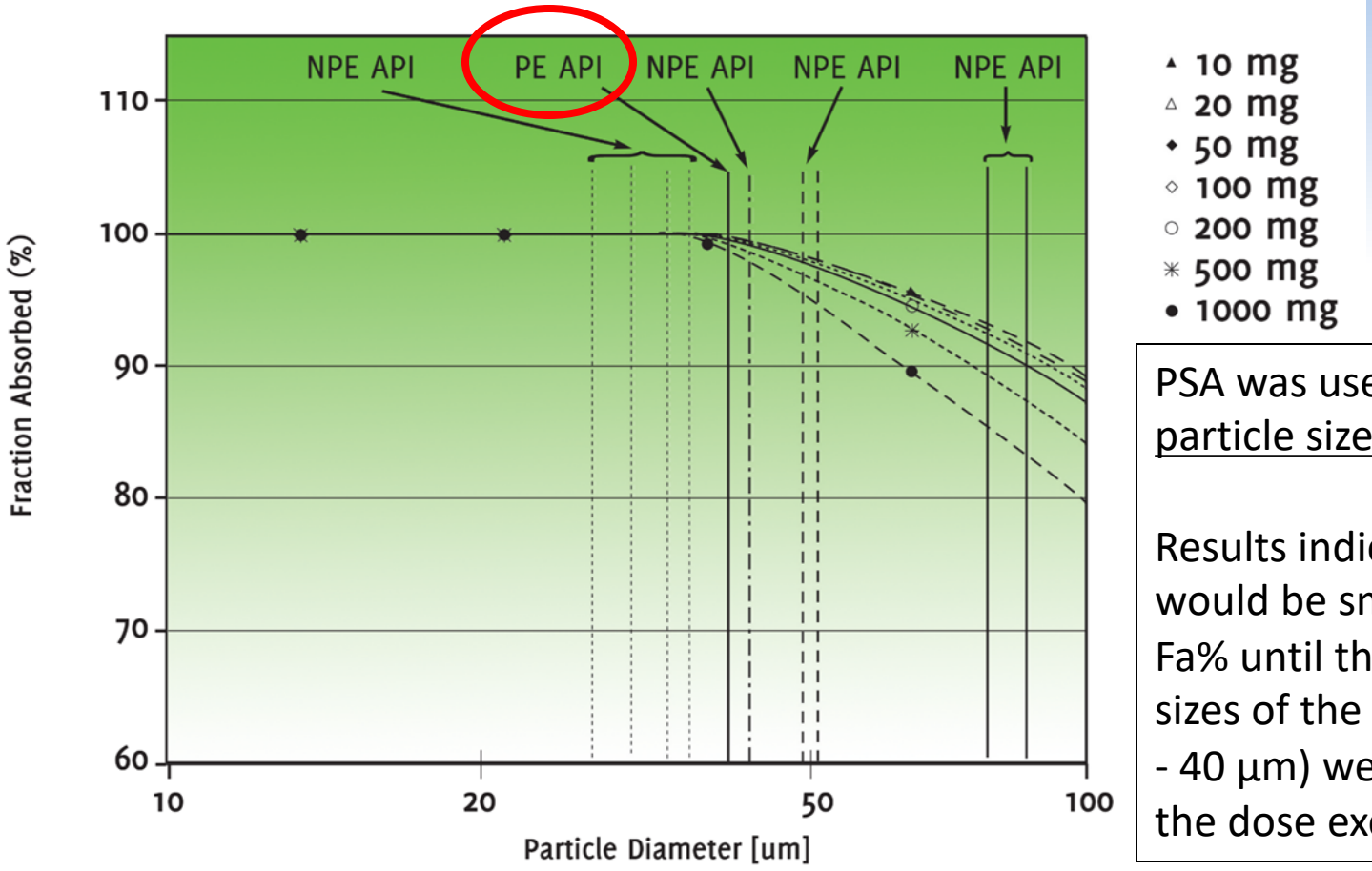
Part II: Parameter Sensitivity Analysis (PSA) Around Mean Particle Radius: Dose Range: 10 – 1000 mg



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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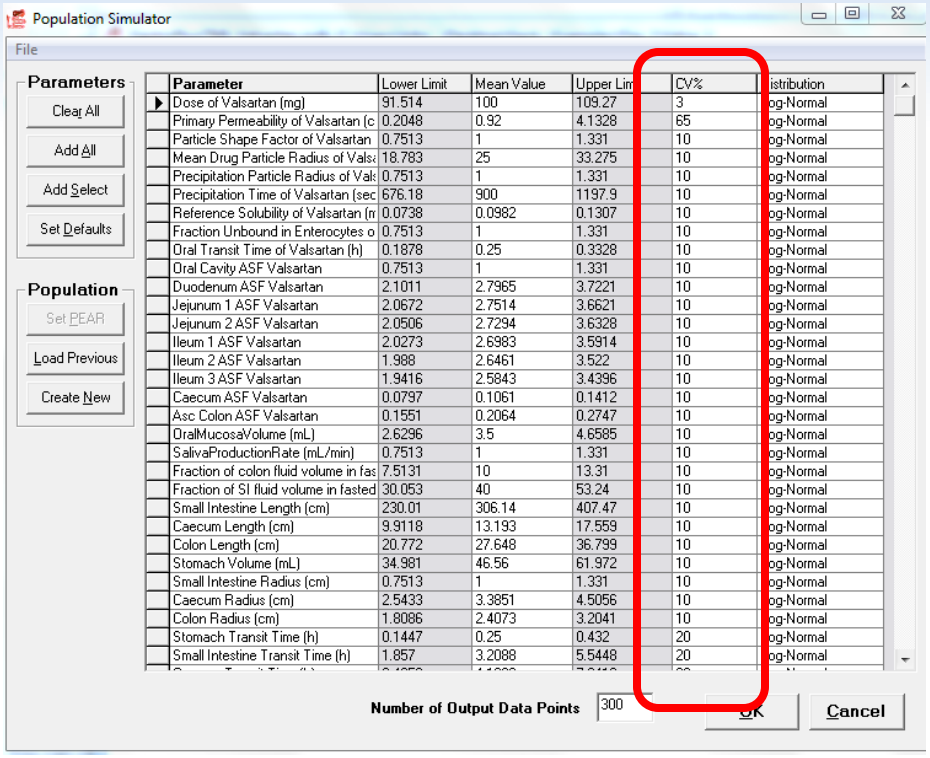
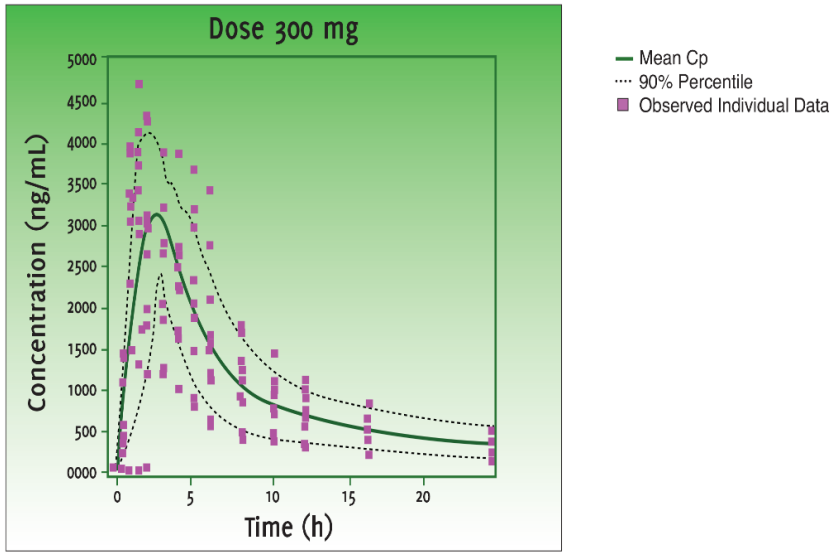
Part III: Virtual Bioequivalence Trials: Population Simulator

- Incorporate measured variability for physicochemical, formulation and PK parameters into Population Simulator
- Capture observed variability from existing clinical PK studies



Parameter	Lower Limit	Mean Value	Upper Lim	CV%	istribution
Dose of Valsartan (mg)	91.514	100	109.27	3	og-Normal
Primary Permeability of Valsartan (c	0.2048	0.92	4.1328	65	og-Normal
Particle Shape Factor of Valsartan	0.7513	1	1.331	10	og-Normal
Mean Drug Particle Radius of Vals	18.783	25	33.275	10	og-Normal
Precipitation Particle Radius of Val	0.7513	1	1.331	10	og-Normal
Precipitation Time of Valsartan (sec	676.18	900	1197.9	10	og-Normal
Reference Solubility of Valsartan (n	0.0738	0.0982	0.1307	10	og-Normal
Fraction Unbound in Enterocytes o	0.7513	1	1.331	10	og-Normal
Oral Transit Time of Valsartan (h)	0.1878	0.25	0.3328	10	og-Normal
Oral Cavity ASF Valsartan	0.7513	1	1.331	10	og-Normal
Duodenum ASF Valsartan	2.1011	2.7965	3.7221	10	og-Normal
Jejunum 1 ASF Valsartan	2.0672	2.7514	3.6621	10	og-Normal
Jejunum 2 ASF Valsartan	2.0506	2.7294	3.6328	10	og-Normal
Ileum 1 ASF Valsartan	2.0273	2.6983	3.5914	10	og-Normal
Ileum 2 ASF Valsartan	1.988	2.6461	3.522	10	og-Normal
Ileum 3 ASF Valsartan	1.9416	2.5843	3.4396	10	og-Normal
Caecum ASF Valsartan	0.0797	0.1061	0.1412	10	og-Normal
Asc Colon ASF Valsartan	0.1551	0.2064	0.2747	10	og-Normal
OralMucosaVolume (mL)	2.6296	3.5	4.6585	10	og-Normal
SalivaProductionRate (mL/min)	0.7513	1	1.331	10	og-Normal
Fraction of colon fluid volume in fas	7.5131	10	13.31	10	og-Normal
Fraction of SI fluid volume in fasted	30.053	40	53.24	10	og-Normal
Small Intestine Length (cm)	230.01	306.14	407.47	10	og-Normal
Caecum Length (cm)	9.9118	13.193	17.559	10	og-Normal
Colon Length (cm)	20.772	27.648	36.799	10	og-Normal
Stomach Volume (mL)	34.981	46.56	61.972	10	og-Normal
Small Intestine Radius (cm)	0.7513	1	1.331	10	og-Normal
Caecum Radius (cm)	2.5433	3.3851	4.5056	10	og-Normal
Colon Radius (cm)	1.8086	2.4073	3.2041	10	og-Normal
Stomach Transit Time (h)	0.1447	0.25	0.432	20	og-Normal
Small Intestine Transit Time (h)	1.857	3.2088	5.5448	20	og-Normal



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Virtual Bioequivalence Study Simulations

API Lot	PE/NPE	Dose (mg)	AUC_{∞} (ng.h/mL) (N=250)		C_{max} (ng/mL) (N=250)	
			GM	GMR (90% CI)	GM	GMR (90% CI)
Lot 5	PE	50	4180	113.3 (110.7, 116.1)	551	139.3 (136.0, 142.7)
Lot 1	NPE	50	3688		395	
Lot 5	PE	100	8242	103.0 (100.9, 105.1)	551	106.4 (104.3, 108.6)
Lot 3	NPE	100	8001		395	
Lot 5	PE	300	24998	102.2 (99.8, 104.6)	3118	100.0 (97.7, 102.4)
Lot 2	NPE	300	24460		3117	
Lot 5	PE	100	8242	98.2 (96.2, 100.2)	1068	95.1 (93.2, 97.0)
Lot 4	NPE	100	8395		1123	
Lot 5	PE	300	24998	101.9 (99.8, 104.1)	3118	98.3 (96.3, 100.4)
Lot 4	NPE	300	24525		3171	

API: active pharmaceutical ingredient; AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ration; NPE: non-particle-engineered; PE: particle-engineered

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

Summary

- A mechanistic, physiologically-based absorption/PK model was constructed in GastroPlus and validated across three dose levels (50, 100, and 300 mg) using *in vivo* data collected from tablets manufactured with non particle-engineered API.

- Parameter sensitivity analysis showed that mean particle size would be the main property that determines whether formulations are likely to be bioequivalent, regardless of dose.

- Virtual bioequivalence trial simulations showed that, for a sufficiently powered study, the population-derived C_{max} and AUC values would be bioequivalent between the tablets manufactured with non particle-engineered (NPE) vs. new particle-engineered (PE) API, up to 40 µm particle size, regardless of the dose.

- **Regulatory agencies approved the sponsor's biowaiver application**
- **Sponsor got to market ~12 months before it would have running the full trials**

Case Study: Justification of Drug Product Dissolution Rate

Justification of Drug Product Dissolution Rate and Drug Substance Particle Size Specifications Based on Absorption PBPK Modeling for Lesinurad Immediate Release Tablets

Xavier J. H. Pepin,[*,†] Talia R. Flanagan,[†] David J. Holt,[†] Anna Eidelman,[‡] Don Treacy,[‡] and Colin E. Rowlings[‡]

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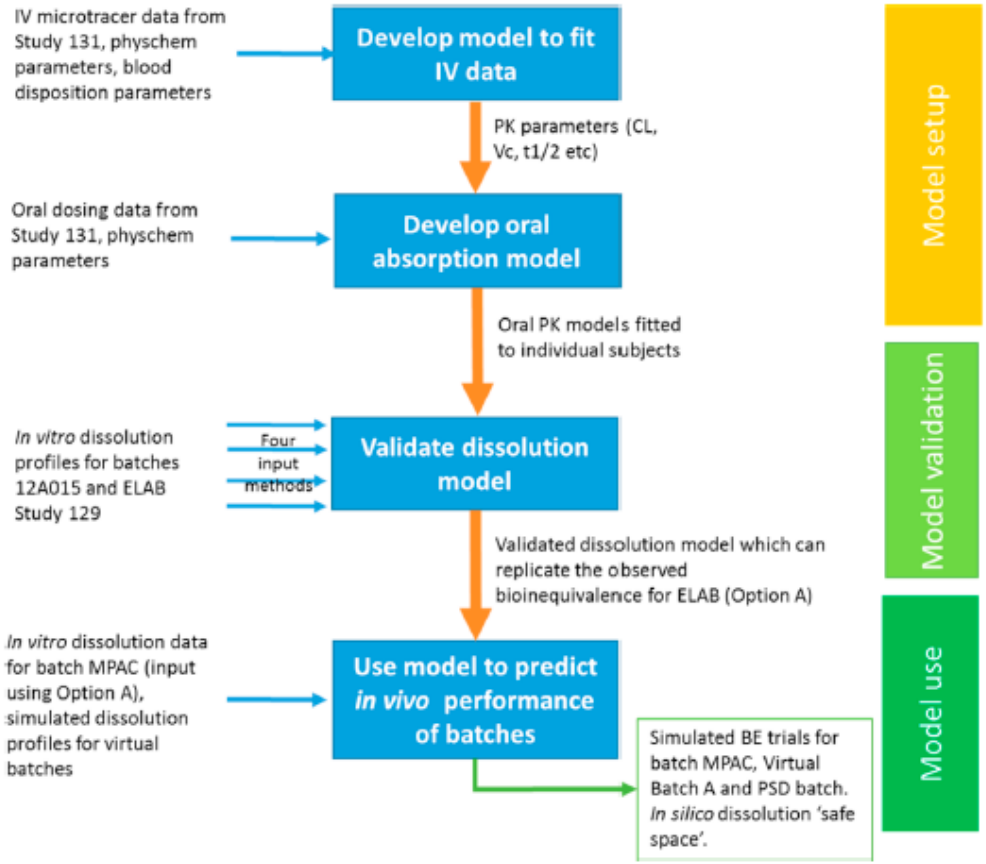
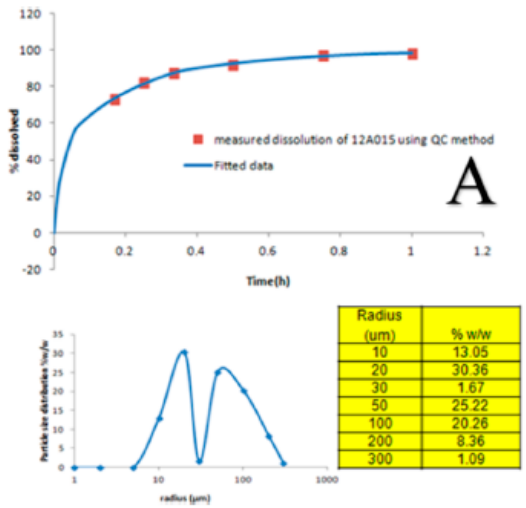
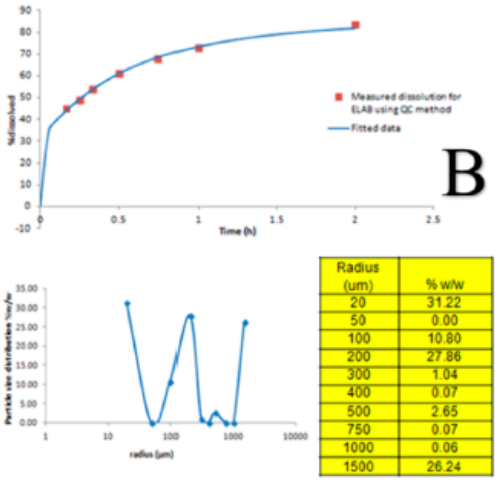


DOI: 10.1021/acs.molpharmaceut.6b00497
Mol. Pharmaceutics 2016, 13, 3256−3269

Theoretical particle size distribution was fitted to *in vitro* dissolution data and used as an input for *in vivo* simulation



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



Radius (um)	% w/w
20	31.22
50	0.00
100	10.80
200	27.86
300	1.04
400	0.07
500	2.65
750	0.07
1000	0.06
1500	26.24

Figure 4. Fitting of dissolution profile for batch 12A015 (A) and ELAB (B) in the QC dissolution method with a theoretical particle size distribution. Note: the value presented at the 2 h time point for batch ELAB is from an infinity spin (15 min, 250 rpm).

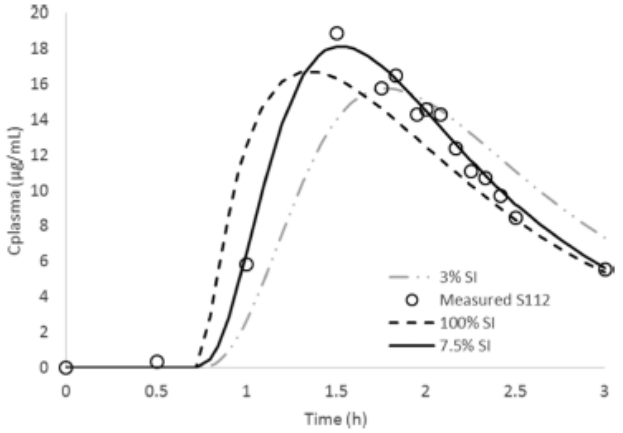


Figure 7. Simulated PK profile vs measured plasma concentrations for S112 following administration of 400 mg 12A015 tablet using Option A.

The *in vitro* dissolution profiles showed multi-phasic behavior for these formulation and could not be successfully fitted with single z-factor.

Fitting "artificial" particle size distribution allowed for more accurate translation of *in vitro* dissolution to *in vivo*

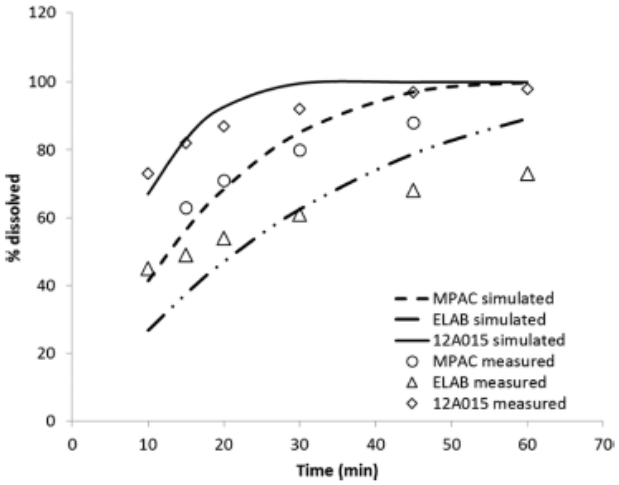


Figure 8. Z-factor fit for batches 12A015 ($Z = 1 \times 10^{-3}$ mL/mg/s), ELAB ($Z = 3.74 \times 10^{-4}$ mL/mg/s), and MPAC (Z = 5e-4 mL/mg/s).

Pepin et al. Mol Pharmaceutics 2016, 13:3256-3269

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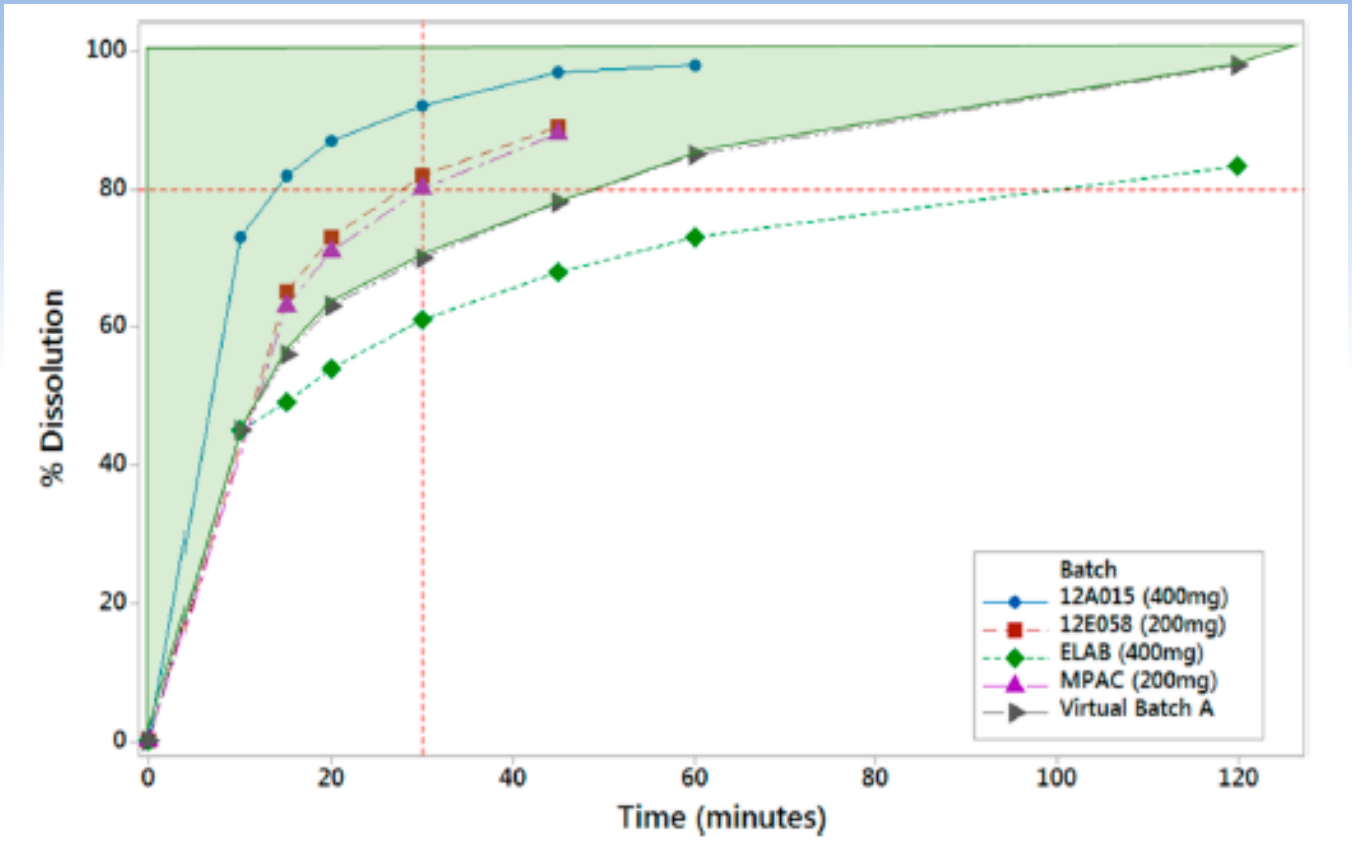
Once validated, the approach was used to determine the dissolution specifications for the formulation



Pepin et al. Mol Pharmaceutics 2016, 13:3256-3269

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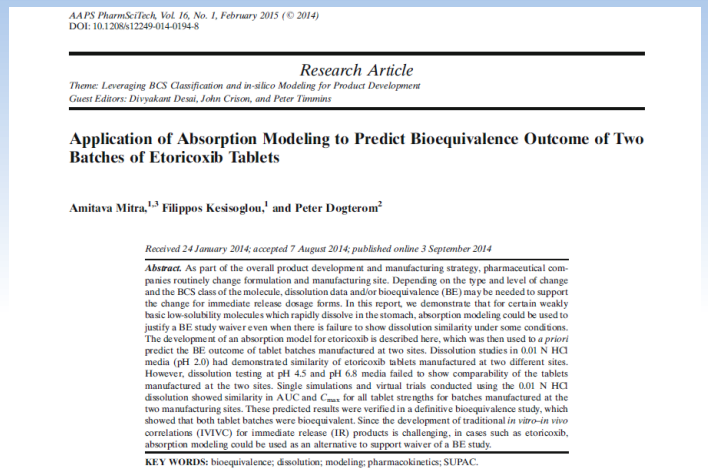
Other Recent Examples: Product Changes & Virtual BE

Mitra et al., AAPS PharmSciTech 2015, 16(1):76



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DOI: 10.1208/s12249-014-0194-8

Research Article

Theme: Leveraging BCS Classification and in-silico Modeling for Product Development
Guest Editors: Divyakant Desai, John Crison, and Peter Timmins

Application of Absorption Modeling to Predict Bioequivalence Outcome of Two Batches of Etoricoxib Tablets

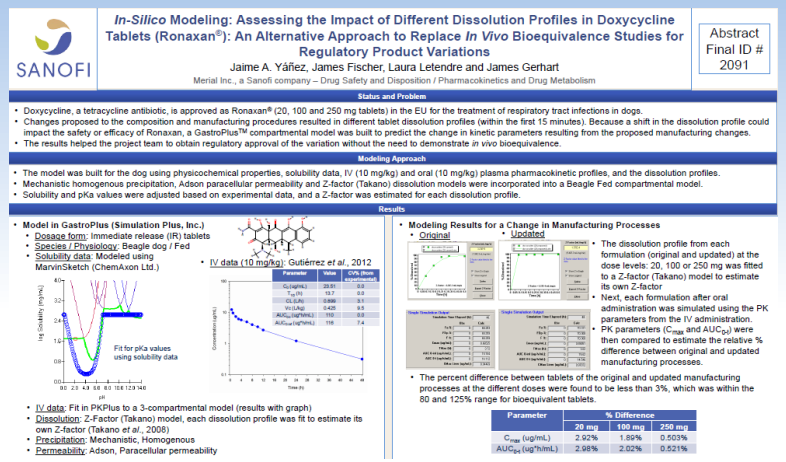
Amitava Mitra,[1,3] Filippos Kesisoglou,[1] and Peter Dogterom[2]

Received 24 January 2014; accepted 7 August 2014; published online 3 September 2014

Abstract. As part of the overall product development and manufacturing strategy, pharmaceutical companies routinely change formulation and manufacturing site. Depending on the type and level of change and the BCS class of the molecule, dissolution data and/or bioequivalence (BE) may be needed to support the change for immediate release dosage forms. In this report, we demonstrate that for certain weakly basic low-solubility molecules which rapidly dissolve in the stomach, absorption modeling could be used to justify a BE study waiver even when there is failure to show dissolution similarity under some conditions. The development of an absorption model for etoricoxib is described here, which was then used to *a priori* predict the BE outcome of tablet batches manufactured at two sites. Dissolution studies in 0.01 N HCl media (pH 2.0) had demonstrated similarity of etoricoxib tablets manufactured at two different sites. However, dissolution testing at pH 4.5 and pH 6.8 media failed to show comparability of the tablets manufactured at the two sites. Single simulations and virtual trials conducted using the 0.01 N HCl dissolution showed similarity in AUC and C_{max} for all tablet strengths for batches manufactured at the two manufacturing sites. These predicted results were verified in a definitive bioequivalence study, which showed that both tablet batches were bioequivalent. Since the development of traditional *in vitro–in vivo* correlations (IVIVC) for immediate release (IR) products is challenging, in cases such as etoricoxib, absorption modeling could be used as an alternative to support waiver of a BE study.

KEY WORDS: bioequivalence; dissolution; modeling; pharmacokinetics; SUPAC.

Yanez et al., SOT Annual Meeting 2015, San Diego, CA



SANOFI

***In-Silico* Modeling: Assessing the Impact of Different Dissolution Profiles in Doxycycline Tablets (Ronaxan®): An Alternative Approach to Replace *In Vivo* Bioequivalence Studies for Regulatory Product Variations**

Abstract Final ID # 2091

Jaime A. Yáñez, James Fischer, Laura Letendre and James Gerhart

Merial Inc., a Sanofi company – Drug Safety and Disposition / Pharmacokinetics and Drug Metabolism

Status and Problem

- Doxycycline, a tetracycline antibiotic, is approved as Ronaxan® (20, 100 and 250 mg tablets) in the EU for the treatment of respiratory tract infections in dogs.
- Changes proposed to the composition and manufacturing procedures resulted in different tablet dissolution profiles (within the first 15 minutes). Because a shift in the dissolution profile could impact the safety or efficacy of Ronaxan, a GastroPlus™ compartmental model was built to predict the change in kinetic parameters resulting from the proposed manufacturing changes.
- The results helped the project team to obtain regulatory approval of the variation without the need to demonstrate *in vivo* bioequivalence.

Modeling Approach

- The model was built for the dog using physicochemical properties, solubility data, IV (10 mg/kg) and oral (10 mg/kg) plasma pharmacokinetic profiles, and the dissolution profiles.
- Mechanistic homogenous precipitation, Adson paracellular permeability and Z-factor (Takano) dissolution models were incorporated into a Beagle Fed compartmental model.
- Solubility and pKa values were adjusted based on experimental data, and a Z-factor was estimated for each dissolution profile.

Results

- **Model in GastroPlus (Simulation Plus, Inc.)**
  - Dosage form: Immediate release (IR) tablets
  - Species / Physiology: Beagle dog / Fed
  - Solubility data: Modeled using MarvinSketch (ChemAxon Ltd.)
  - IV data (10 mg/kg): Gutiérrez *et al.*, 2012
  - Fit for pKa values using solubility data
  - IV data: Fit in PKPlus to a 3-compartmental model (results with graph)
  - Dissolution: Z-Factor (Takano) model, each dissolution profile was fit to estimate its own Z-factor (Takano *et al.*, 2008)
  - Precipitation: Mechanistic, Homogenous
  - Permeability: Adson, Paracellular permeability
- **Modeling Results for a Change in Manufacturing Processes**
  - Original
  - Updated
  - The dissolution profile from each formulation (original and updated) at the dose levels: 20, 100 or 250 mg was fitted to a Z-factor (Takano) model to estimate its own Z-factor
  - Next, each formulation after oral administration was simulated using the PK parameters from the IV administration.
  - PK parameters (C_{max} and $AUC_{0\infty}$) were then compared to estimate the relative % difference between original and updated manufacturing processes.
  - The percent difference between tablets of the original and updated manufacturing processes at the different doses were found to be less than 3%, which was within the 80 and 125% range for bioequivalent tablets.

Parameter	% Difference		
	20 mg	100 mg	250 mg
C_{max} (ug/mL)	2.92%	1.86%	0.503%
$AUC_{0\infty}$ (ug*h/mL)	2.98%	2.02%	0.521%

RESEARCH ARTICLE – *Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism*

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

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

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24474

ABSTRACT: Amphetamine (AMP) salts-based extended-release (ER) drug products are widely used for the treatment of attention deficit hyperactivity disorder. We developed physiologically based absorption models for mixed AMP salts ER capsules and dextroamphetamine sulfate ER capsules to address specific questions raised during generic drug postmarketing surveillance and bioequivalence (BE) guidance development. The models were verified against several data sets. Virtual BE simulations were conducted to assess BE in various populations other than normal healthy subjects where BE studies are generally conducted for approval. The models were also used to predict pharmacokinetics (PK) for hypothetical formulations having dissolution profiles falling within specification after the development of *in vitro–in vivo* relation. Finally, we demonstrated how to use the models to test sensitivity of PK metrics to the changes in formulation variables. Published 2015. This article is a U.S. Government work and is in the public domain in the USA J Pharm Sci

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

Babiskin et al., J. Pharm. Sci. 2015, 104(9):3170

Virtual population pharmacokinetic using physiologically based pharmacokinetic model for evaluating bioequivalence of oral lacidipine formulations in dogs

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Yang et al., Asian J. Pharm. Sci. 2016; Mar 21

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Bioequivalence of Complex Generic Products

For locally acting drugs (LADs) such as dermatological, ocular, and inhalation products, clinical endpoint bioequivalence (CEBE) studies are often recommended instead of standard PK BE studies. However, many clinical endpoints are not sensitive in reflecting formulation-related differences in drug delivery to the site of action for LADs. This leads to large CEBE studies with potentially false conclusion of BE between two products.

PBBM/PBPK modeling and simulation is a tool to address bioequivalence-related challenges associated with alternative routes of delivery, such as ocular, nasal-pulmonary, and transdermal.

Clin Pharmacol Ther. 2019 Feb;105(2):295-297. doi: 10.1002/cpt.1244. Epub 2018 Nov 19.

Clinical Endpoint Bioequivalence Studies Are Not Sensitive: A Perspective From Generic Drugs.

Novakovic J[1], Szirtes J[1], Fields A[1], Tsang YC[1].

Conclusions

Evolving relationship between *in silico* tools and R&D

- **Model "supported" (first questions 20 years ago)**: Do you think modeling and simulation might help?
- **Model "based" (current questions today)**: How can I maximize the value of modeling and simulation in my development program?
- **Model "driven" (future questions)**: How do I change the R&D process to reflect the availability of *in silico* tools and techniques?

How PBBM modeling & simulation can save resources in R&D

- Prioritize experiments to be done – **better invest resources**
- Integrate the wide variety of data obtained from *in silico*, *in vitro* and *in vivo* experiments to **tell a compelling story**
- **Reduce regulatory burden**
- Productivity tools – be the **first to market**

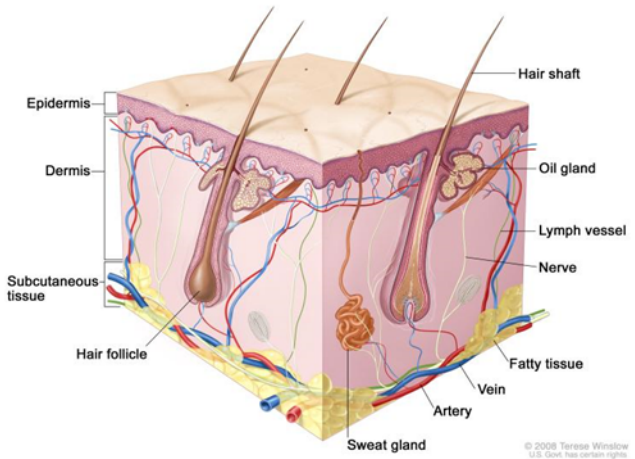
Additional Slides

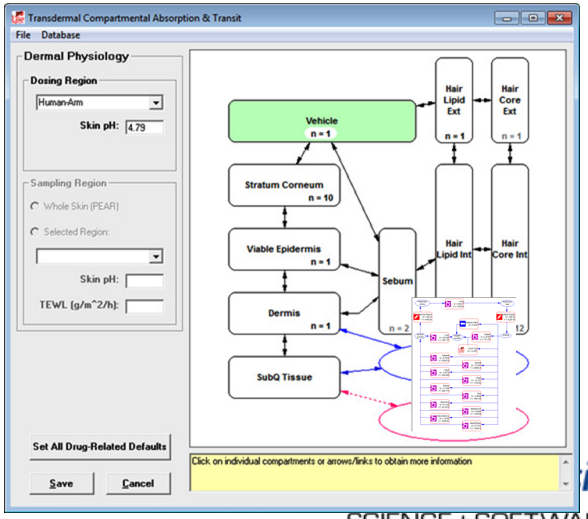
Some of Our International Pharma Customers (total > 250)

Regulatory Interactions & Collaborations

Cooperation Grant with Cosmetics Europe (2018-20)

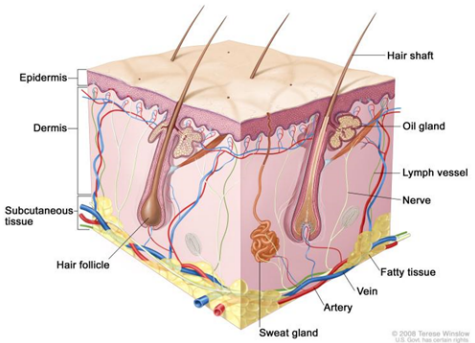
- 1-year *funded* collaborative project with Cosmetics Europe on the enhancement & validation of GastroPlus mechanistic dermal models:
  - Compound evaporation kinetics
  - Improved partition coefficient predictions
  - Saturable metabolism kinetics within the skin

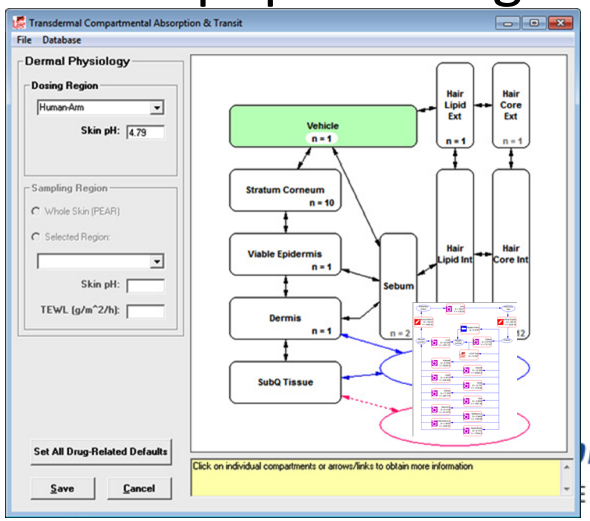




Cooperation Grant with the FDA (2018-20)

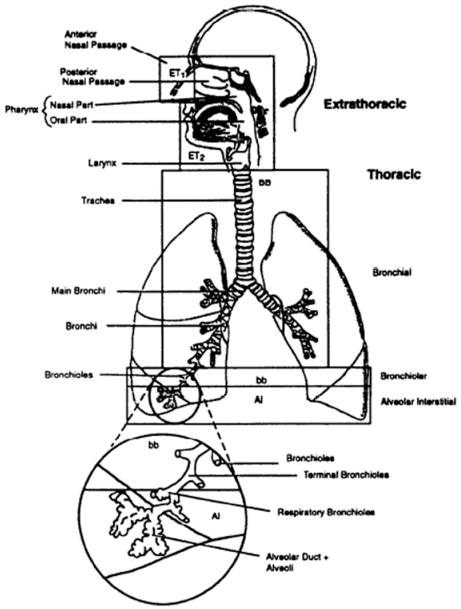
- 2-year *funded* collaborative project with the FDA Office of Generic Drugs on the incorporation of drug product quality attributes into the GastroPlus mechanistic dermal models:
  - Develop mechanistic equations describing *in vitro* release/permeability assays for topical formulations
  - Develop models for various APIs in different population groups

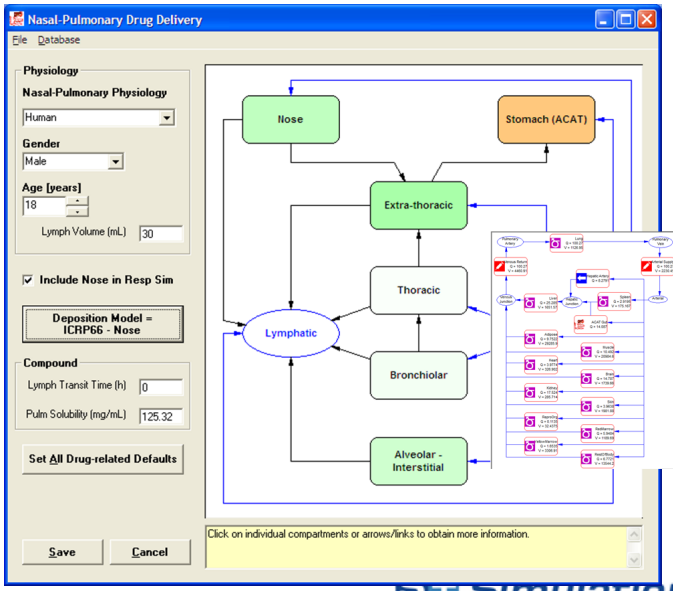




Collaboration Grant with Large Pharmaceutical Company (2019-20)

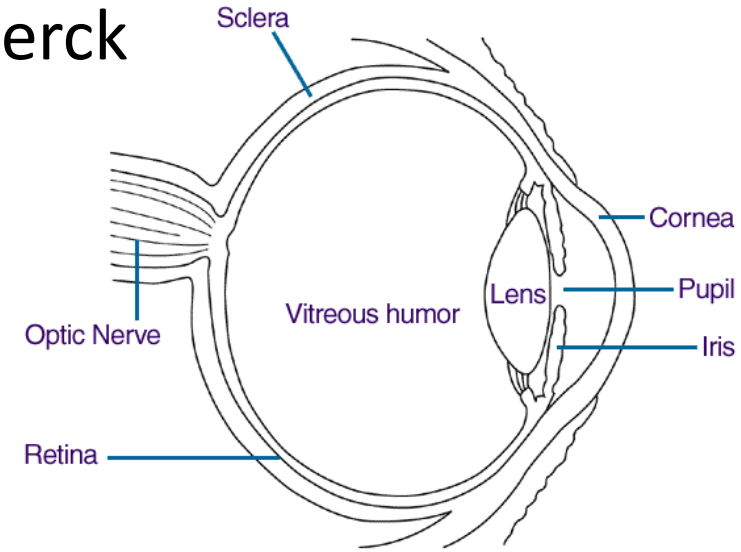
- 2-year *funded* collaborative project with a large pharmaceutical company on the enhancement & validation of GastroPlus mechanistic pulmonary models:
  - Handle volatile materials/vapors
  - Improved deposition predictions through ion trapping effects

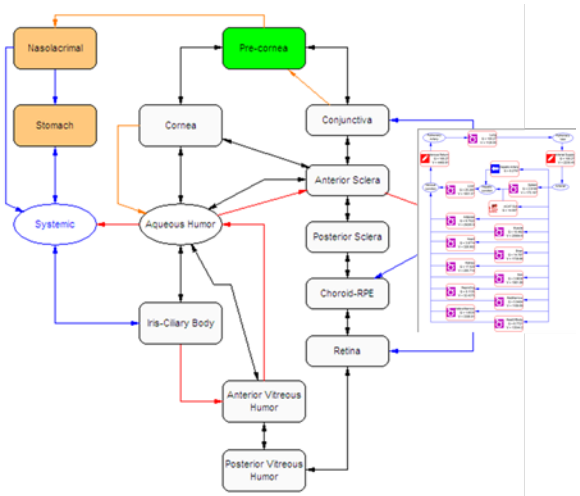




Cooperation Grant with the FDA (2014-20)

- 6-year *funded* collaborative project with the FDA Office of Generic Drugs on the further development & validation of GastroPlus mechanistic models for ocular delivery
- Consortium members: FDA, Alcon, Santen, GSK, Senju, Merck





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Research Collaboration Agreement with the FDA (2014-19)

- 5-year collaborative project with the FDA Office of Testing and Research on the utility of GastroPlus Mechanistic Absorption Modeling (MAM) and IVIVCs to predict complex absorption characteristics
  - Goal is to facilitate drug product development by decreasing regulatory burden through modeling & simulation

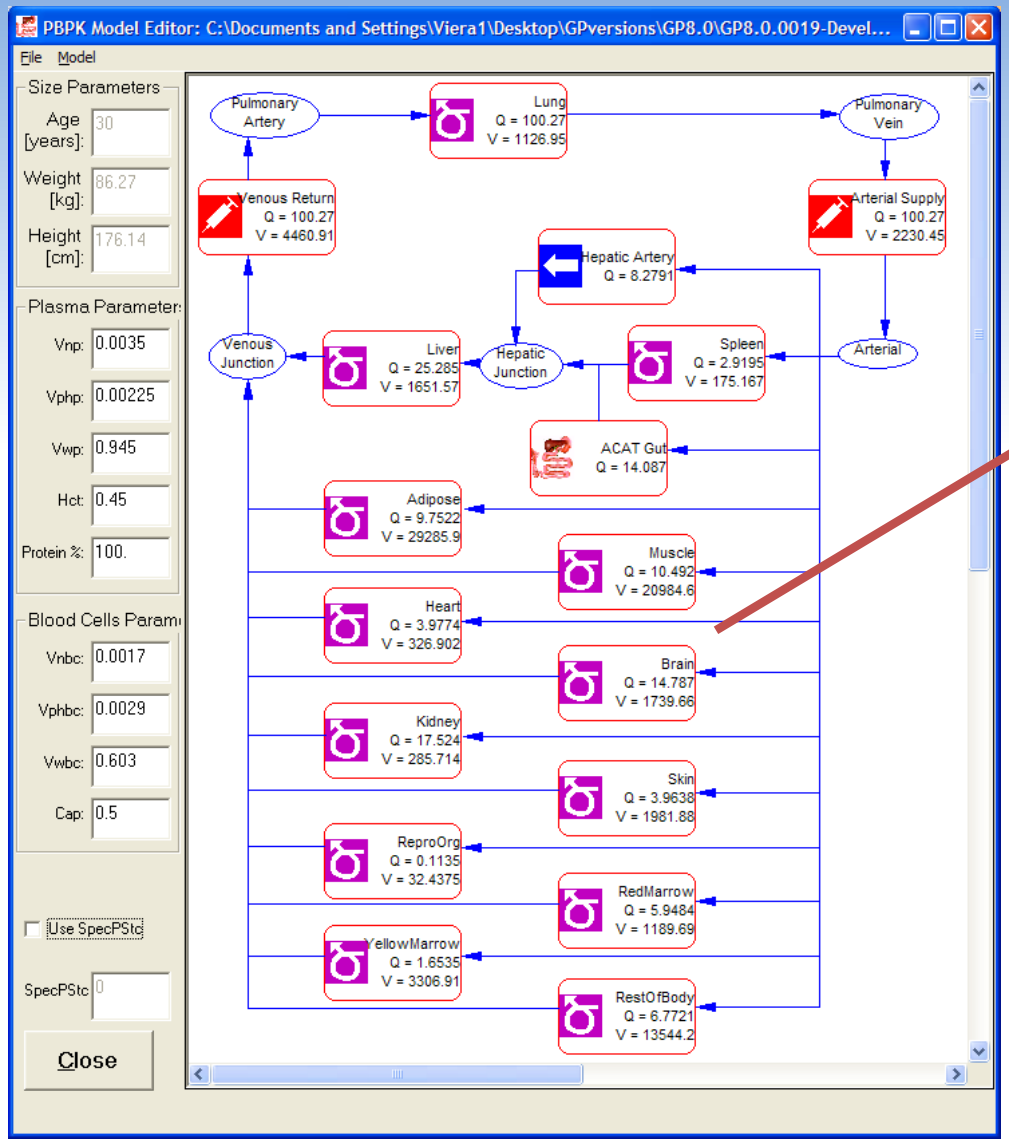
The Virtual BE Trial Simulator™ Project

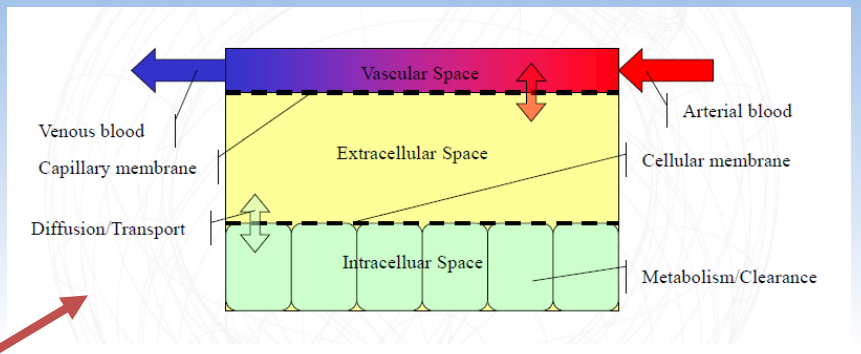
- New funded collaboration with large pharma sponsor:
  - Automation of multiple virtual BE trial simulations w/specific trial designs
  - Integration of intrasubject variability methods
  - Improved statistical analyses and reporting options
  - Implementation of CMC and physiological covariate models
  - Incorporation of audit trails for the virtual BE trial simulation activities
  - Population parameter fitting to link pharmacometrics and PBPK modeling approaches
- First version likely available in summer 2020

Improvements to the ACAT™ Model

- New funded collaboration with large pharma sponsor:
  - Literature review to identify mechanisms, develop and parameterize models to improve predictions of drug concentrations in gut tissue
  - Add option to modify gut perfusion to account for increased liver blood flow under fed conditions
  - Mechanistically model luminal conversion processes
  - Permit the use of observed gut lumen, enterocyte, and whole gut tissue concentrations as target profiles for optimization of model parameters in GastroPlus.
  - Characterize mechanisms leading to drug distribution between the enterocyte layer, gut vascular space and gut tissue
- First version likely available in summer 2020

What's Defined in a PBPK Model?



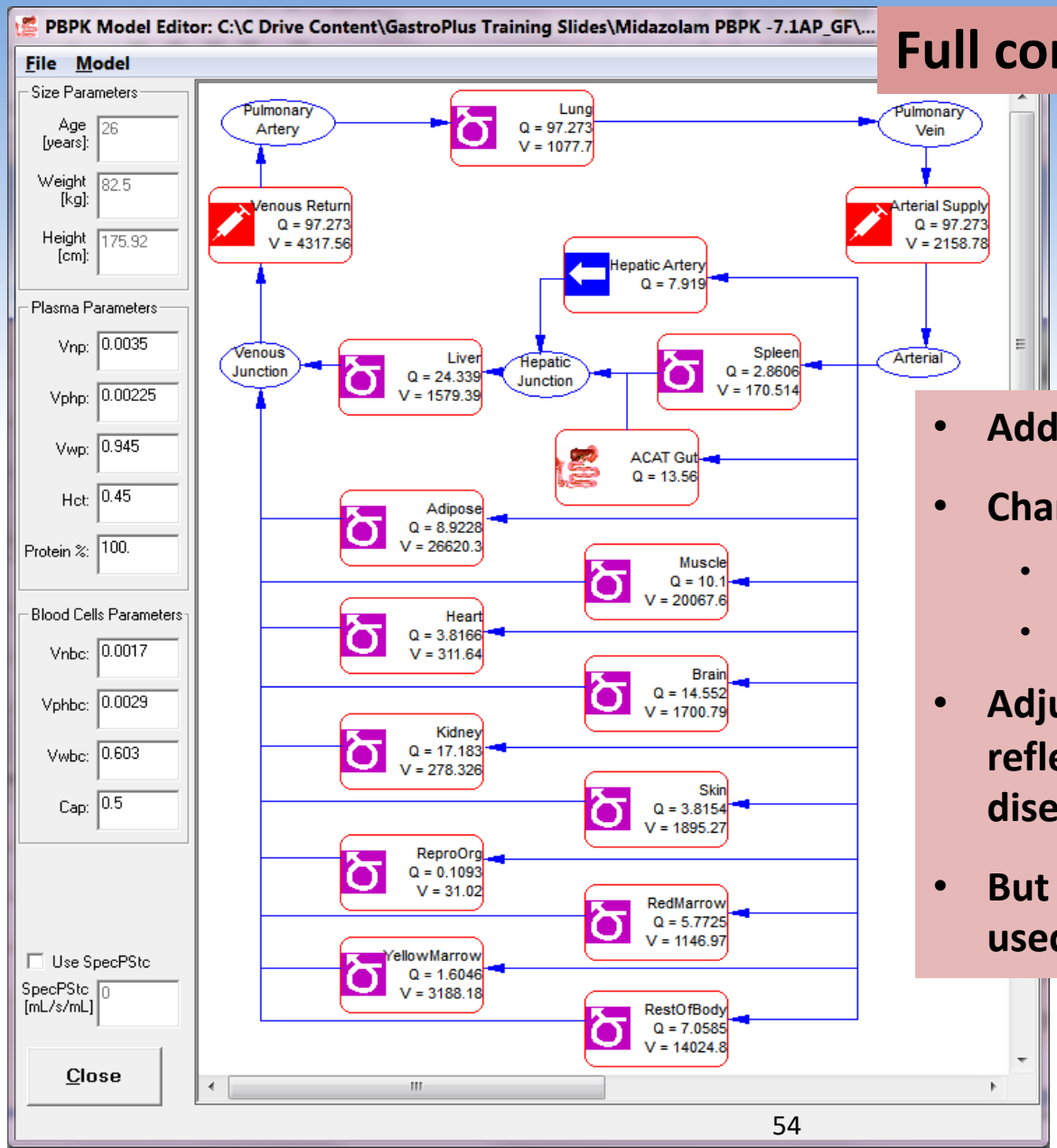


$$Vt\frac{dCt}{dt} = \left(Q \times Cbi - \frac{Q \times Ct \times R_{bp}}{Kp} - CL_{int,u}\left(\frac{Ct \times fu_p}{Kp}\right)\right)$$

- 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)
    - Estimated from drug properties:
      - logD vs. pH
      - pKa(s)
      - Plasma protein binding
      - Blood:plasma concentration ratio

* From literature sources

PBPKPlus Module



Full control over the physiology

- Add or remove tissues
- Change tissue type
  - Perfusion-limited tissue
  - Permeability-limited tissue
- Adjust tissue parameters to reflect different physiology, disease state, …
- But default settings are used most often

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PBPK Modeling of Biologics

Drug Specific Parameters

Vascular reflection coefficient
Lymphatic reflection coefficient
Vascular Rate Fraction
Endosomal Uptake Rate
Recycle Rate
Kon, FcRn
Koff, FcRn
Kdeg
Antigen Kon
Antigen Koff
Antigen Kint

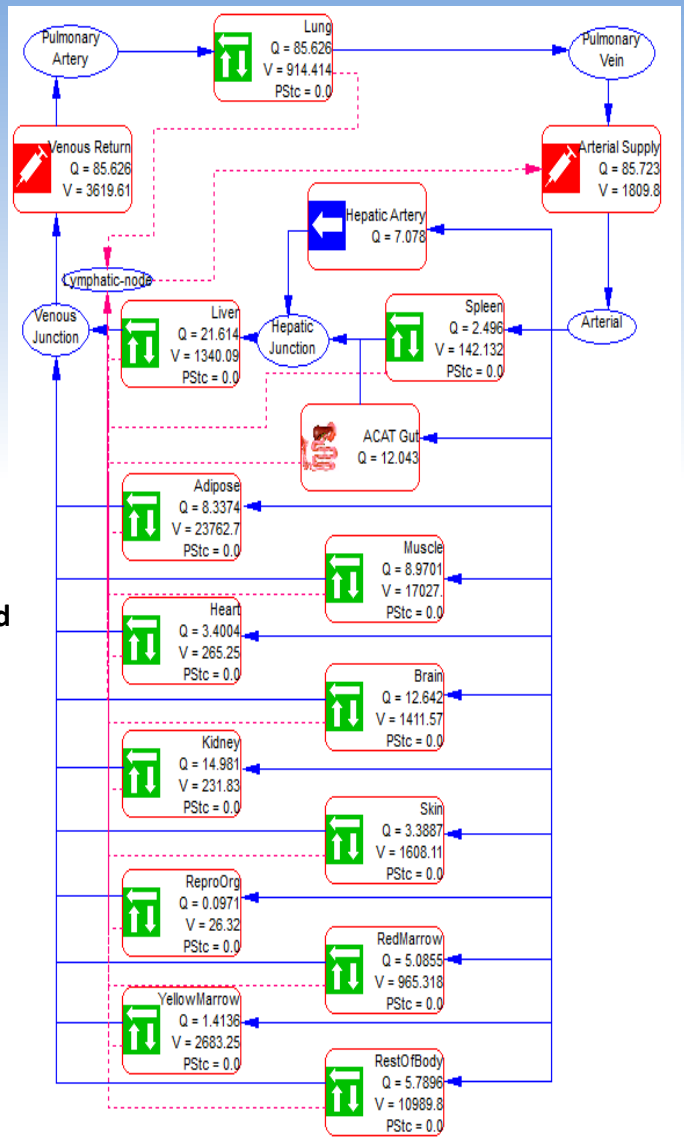
(bold indicates parameters that may be optimized based on available data)

PBPK

Physiological Parameters

Organ size
Tissue composition
Blood perfusion rate
Lymph flow rate
FcRn concentration

Age
Species
Gender
Weight



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Application Areas at the FDA Office of Generic Drugs (2008-2016)

	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)* • *Used to 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)