Incorporating physiologically based pharmacokinetic (PBPK) modeling to assist with Dissolution Method Development, IVIVC & Successful Biowaivers

Dr. Parizad Elchidana

Independent Consultant

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Simulations Plus (NASDAQ: SLP)

- Lancaster, California (**Simulations Plus**)
  - Incorporated in 1996
  - ~35 employees
  - Focused on software development, PBPK modeling & simulation, and QSAR modeling
- Buffalo, New York (**Cognigen**)
  - Incorporated in 1992
  - ~35 employees
  - Focused on software development and pharmacometric services
- Research Triangle Park, North Carolina (**DILIsym Services**)
  - Incorporated in 2015
  - ~10 employees
  - Focused on system toxicology modeling

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Collaboration with ELECTROLAB

- Simulations Plus has partnered with Electrolab
  - Will provide local sales & Tier 1 technical support

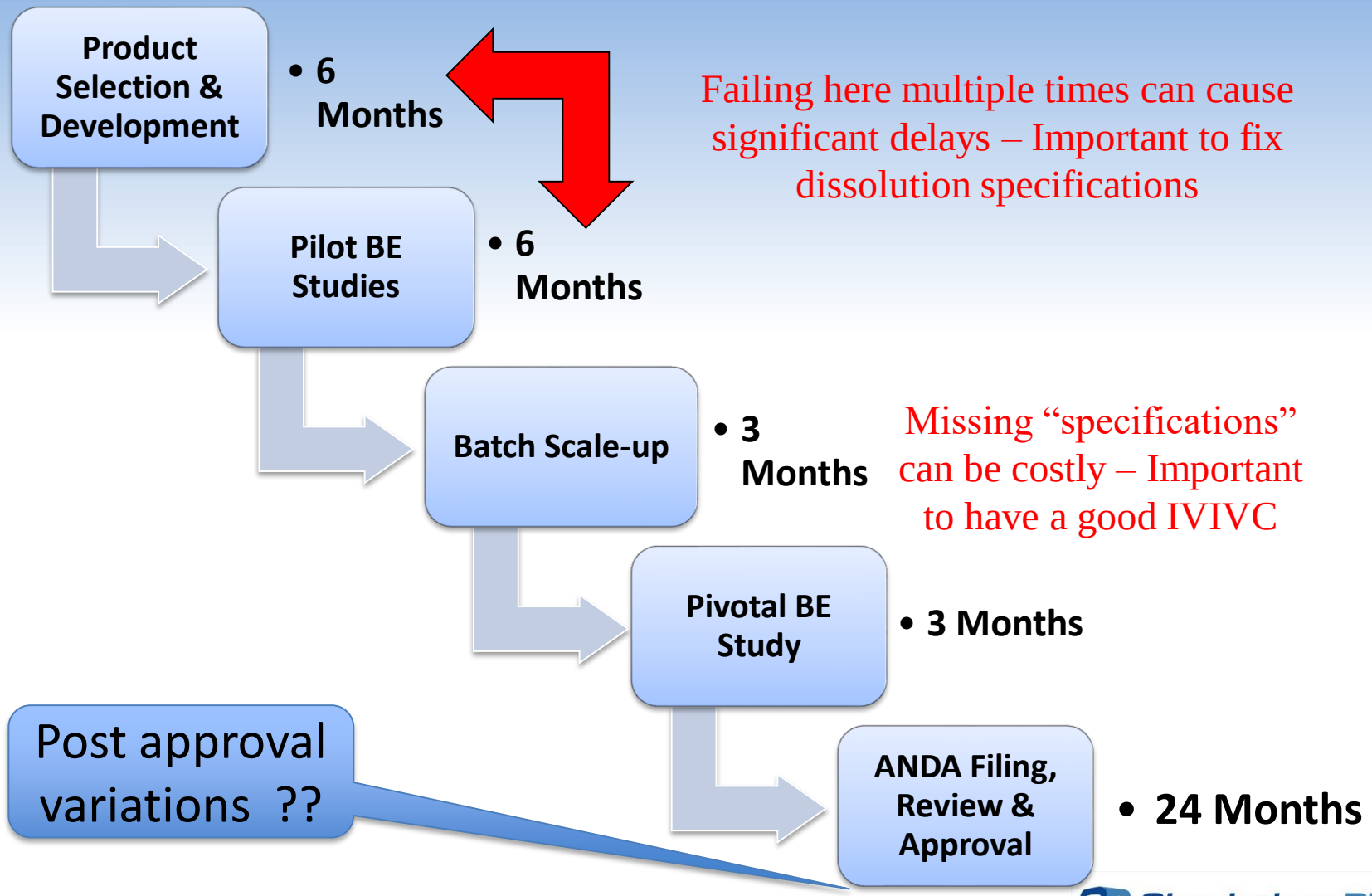
- Electrolab, established in 1984, is a leading provider of dissolution and allied equipment in India with a presence in most pharmaceutical companies
  - Extensive technical sales and support network allows for prompt local support

For more information, visit www.electrolabgroup.com

Outline

- Overview of Generic Product Development Process
- Gastro Plus – The Big Picture
- Advanced Compartmental Absorption & Transit Model **ACAT™.**
- Dissolution Method Development using **DDDPlus™.**
- *Developing a mechanistic in vitro-in vivo correlation (IVIVC)* - A successful biowaiver case study for re-engineered formulation
- Future Directions

The Generic Product Development Process



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Simulations Plus: end-to-end M&S solutions provider

ADMET Predictor™ ⟷ GastroPlus™

- MedChem Studio™
  MedChem Designer™
- DDDPlus™
  MembranePlus™
- PKPlus™
- KIWI™
- DILIsym™
- NAFLDsym™

Consulting Services and Collaborations

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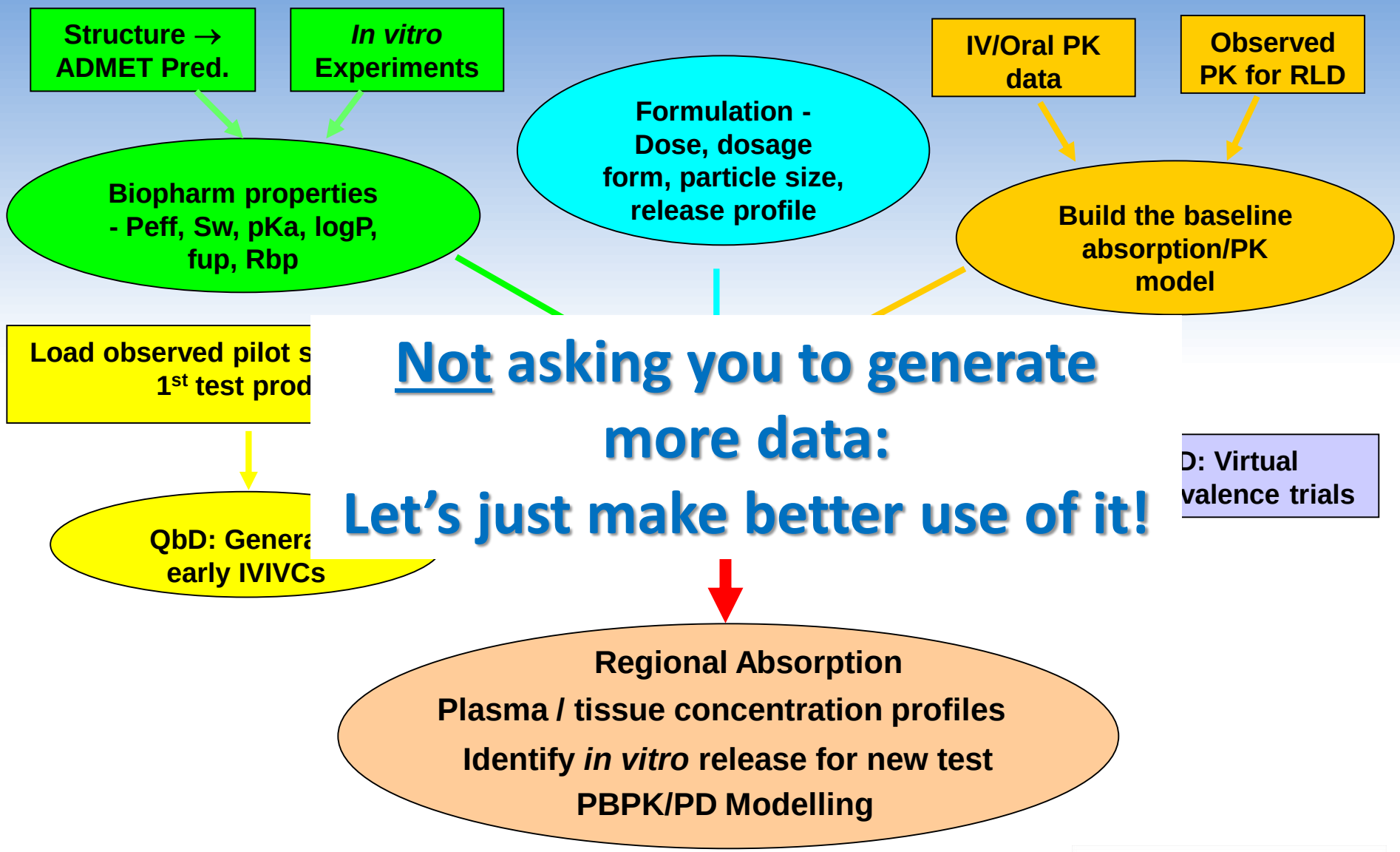
The Big Picture



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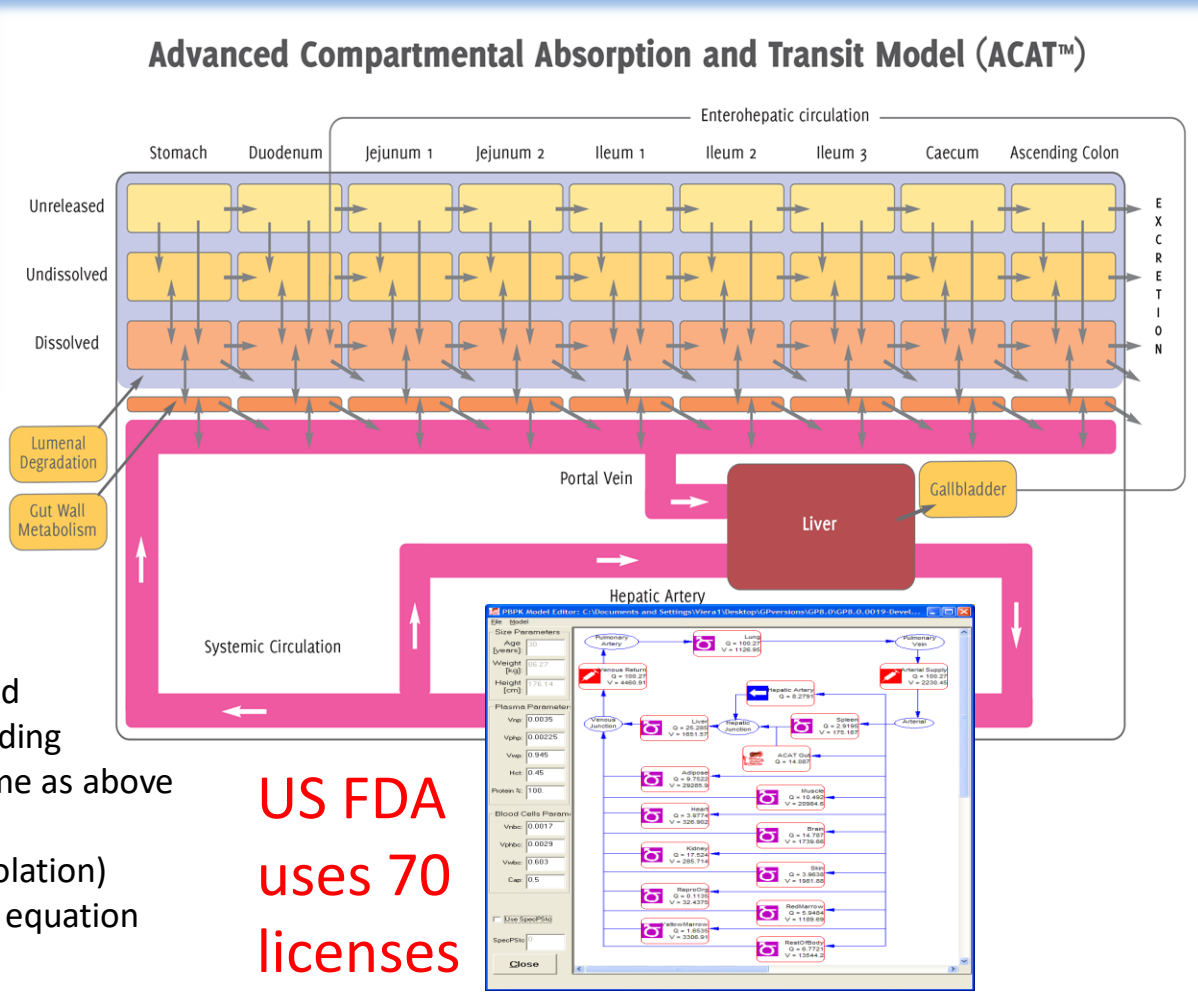
Why is GastroPlus™ unique?

Absorption & Dissolution:

- #1-ranked commercial QSAR models integrated
- #1-ranked commercial model for absorption rate calculations
- Several dissolution models – including the popular Z-factor approach
- Mechanistic nucleation/growth precipitation model
- Paracellular permeability
- Animal physiology models – dog, rat, mouse, cyno & rhesus monkeys, minipig, rabbit
- It's not just gut!



PBPK Modeling:

- #1-ranked Kp calculation method
- Adjustments of plasma lipid binding
- Animal physiology models – same as above
- Unlimited metabolite tracking
- Transporter-based IVIVE (extrapolation)
- Customization of model without equation writing

US FDA uses 70 licenses

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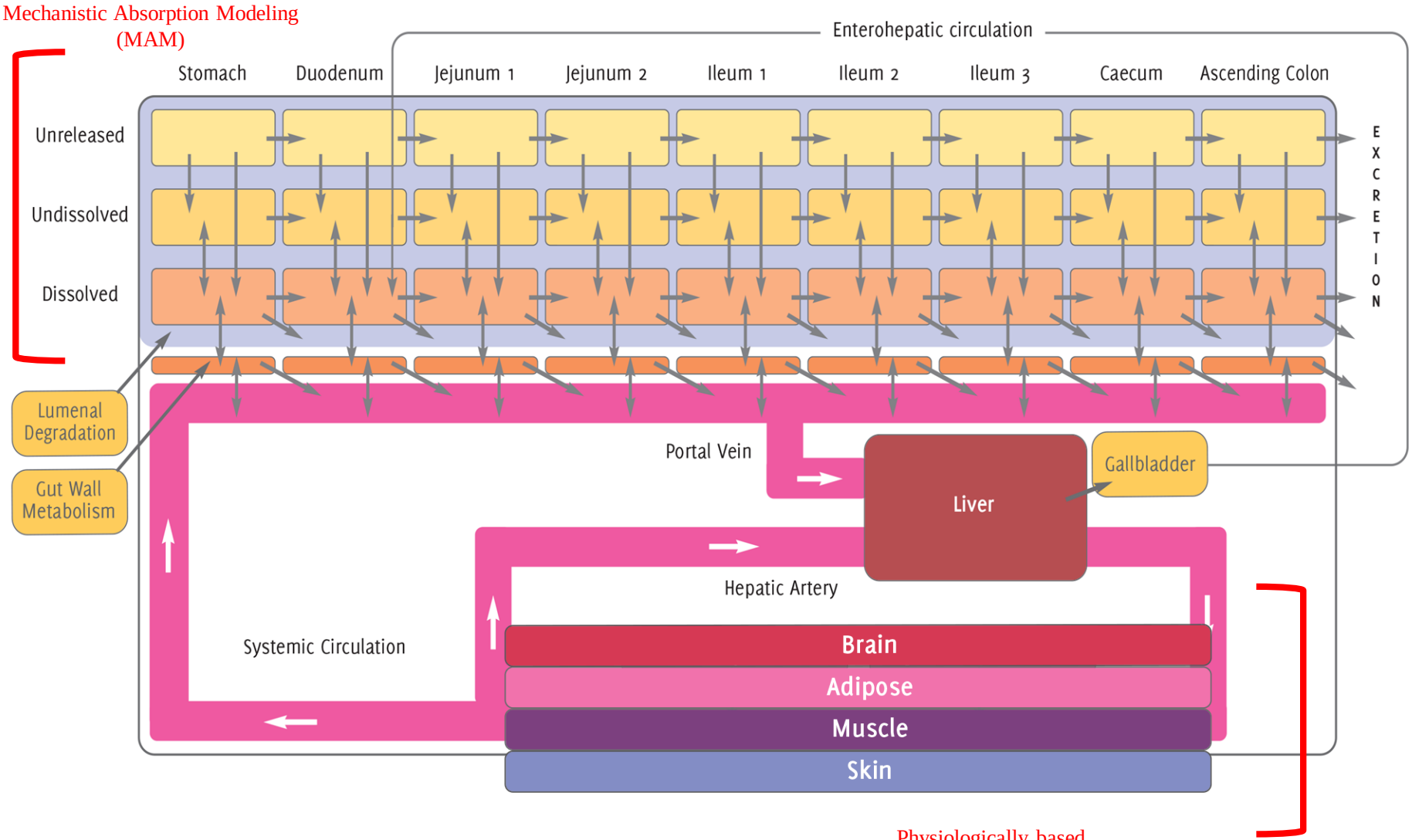
Advanced Compartmental Absorption and Transit Model (ACAT™)



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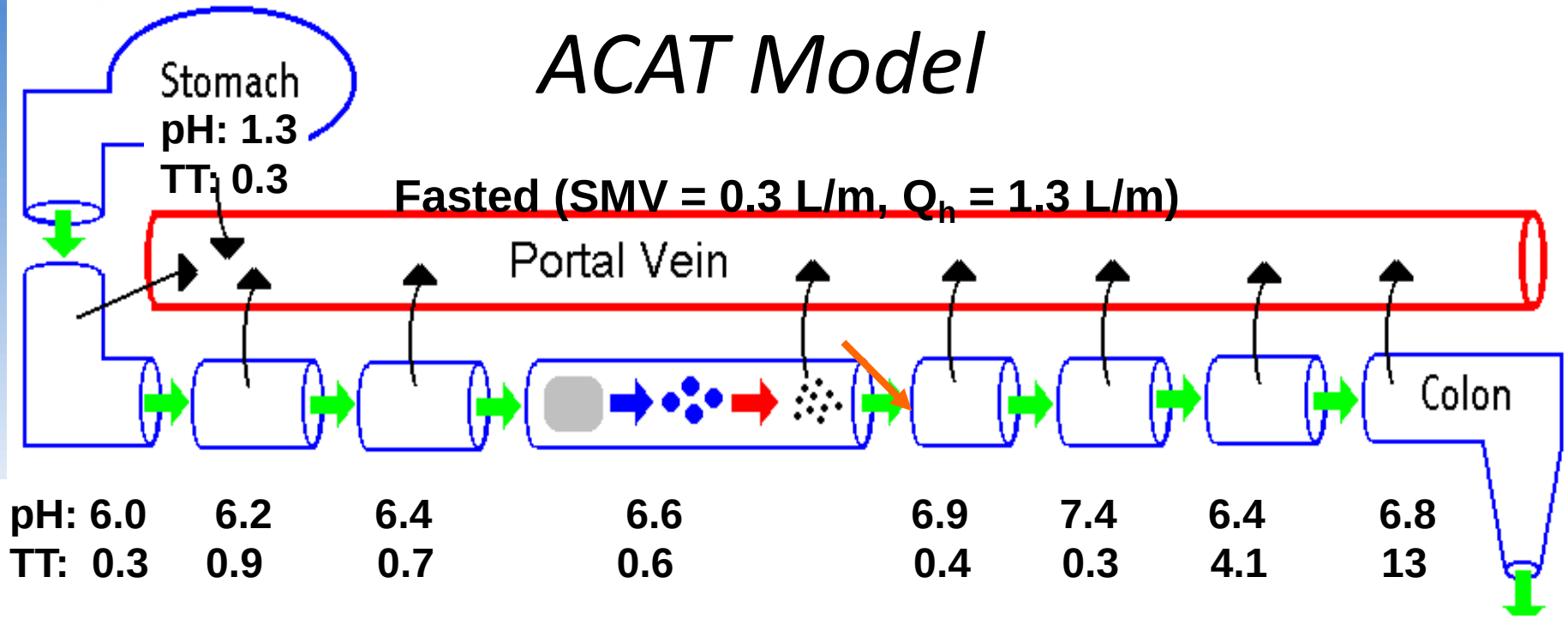
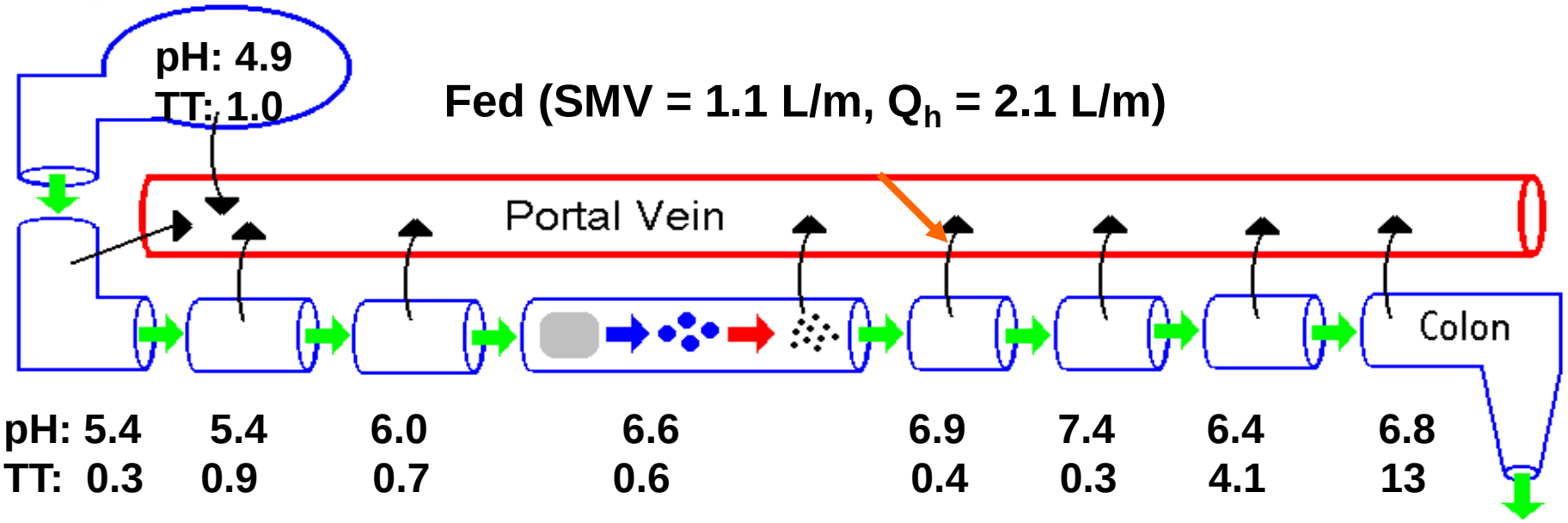
ACAT Model





SMV=superior mesenteric vein Q_h = Liver blood flow

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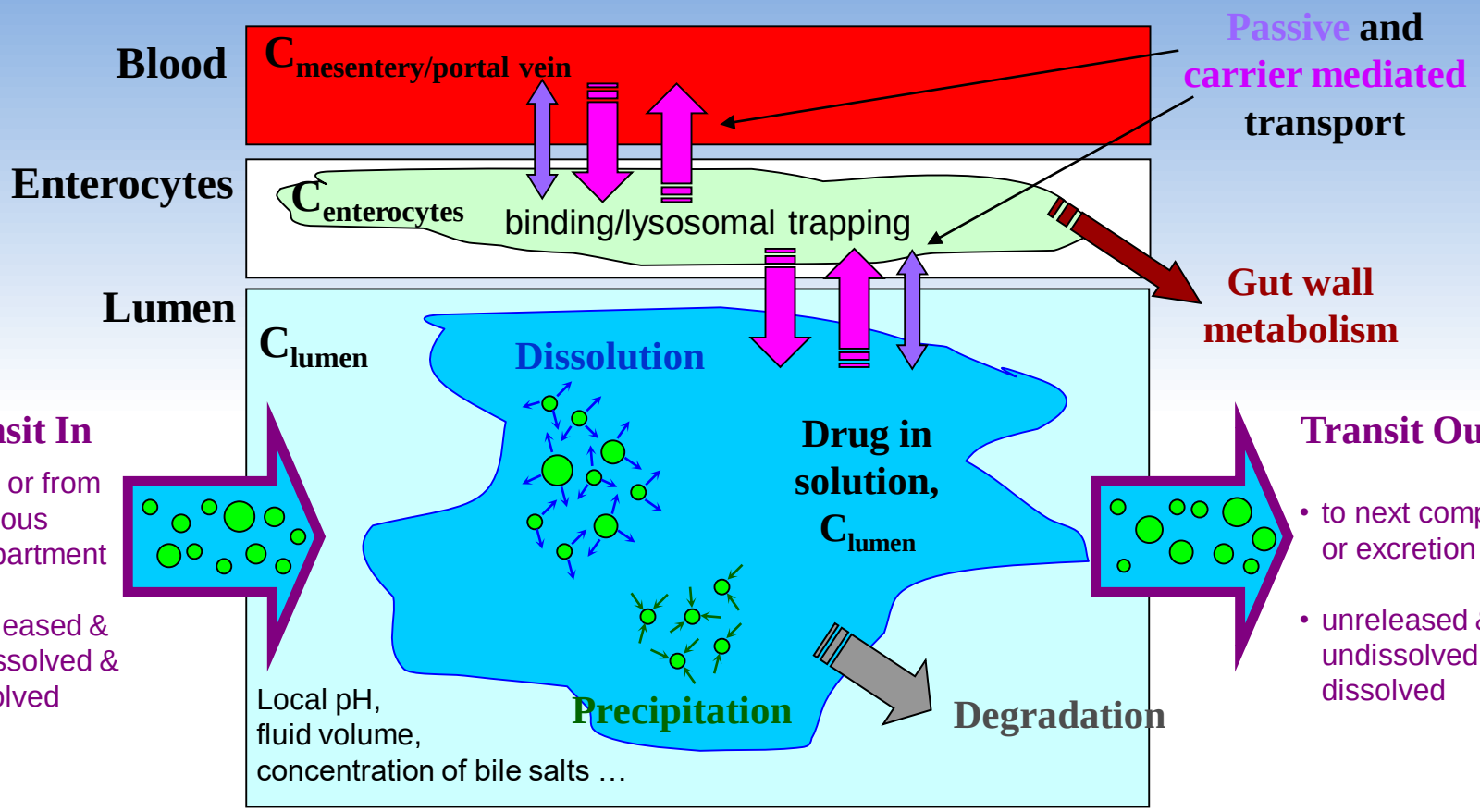
Processes Involved in Oral Absorption



These phenomena:

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

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Dissolution Method Development using **DDDPlus™**

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Utilize modeling and simulation to..

- Integrate with GastroPlus™ absorption/PBPK models to optimize formulations and generate mechanistic IVIVCs – better extrapolation of dissolution inputs for PBPK models
- Assist with dissolution method development
- Assess various formulation strategies to achieve a target *in vitro* dissolution profile
- Apply virtual 'lot-to-lot' variability effects to help establish dissolution specifications – remove the 'guesswork' associated with the identification of dissolution variability and its impact on PK exposure

DDDPlus (Dose Disintegration and Dissolution Plus)

- DDDPlus is an advanced computer program for formulation scientists to simulate the *in vitro* disintegration and dissolution of active pharmaceutical ingredients (API) and excipients under various experimental conditions.

- For new API, a single calibration experiment is all that is needed, after which DDDPlus will predict how changes in formulation or experimental parameters will affect the dissolution rate

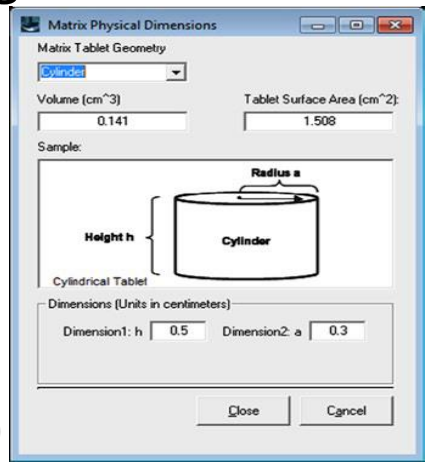
- With DDDPlus, you no longer have to rely on ‘cut and try’ methods to finalize a formulation design.

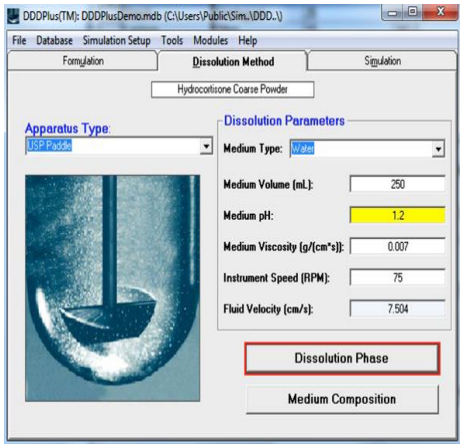
DDDPlus models the following dosage forms:

- Powders
- Capsules
- Tablets
- Polymer Matrix (Swellable & Non-Swellable)
- **NEW!** Coated beads
- **NEW!** Bilayer tablets
- **NEW!** Delayed release coated tablets

4 USP experimental apparatus are defined, with estimates of fluid velocity and hydrodynamic effects for each:

- USP Paddle
- USP Basket
- USP Flow Thru Cell (App 4) (closed and open loop options)
- Rotating Disk
- **NEW!** Pion uDiss Profiler™





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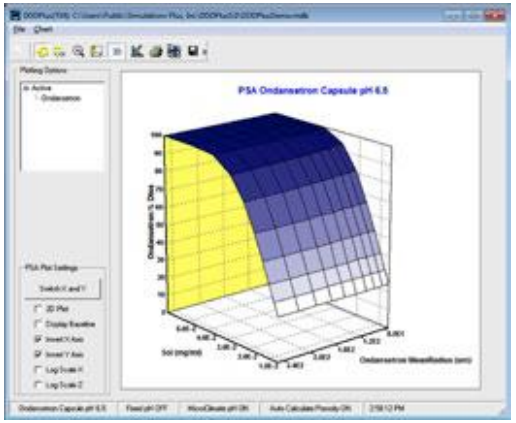
Simulation Modes

Single Simulation: based on compound properties (whether measured or predicted through the ADMET Predictor Module), formulation information, and in vitro dissolution setup, easily run a simulation to predict the time course changes in amount (or percent) dissolved for any ingredient in the product. Also track changes in microclimate and bulk pH levels vs. time.

Parameter Sensitivity Analysis (PSA): select any formulation or experimental parameters to assess the impact of changes on the in vitro dissolution vs. time profiles



NEW! 3D PSA – now analyze the impact of changes in a 'design space' by simulating all combinations of any two selected parameters. Quickly identify an optimal combination that achieves the desired dissolution result

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Experimental Setup

Dissolution Method Conditions and Multi-Phase Experiments

With DDDPlus, you can define your dissolution method conditions like apparatus, instrument speed, medium volume and medium type.

DDDPlus calculates the fluid velocity automatically based on the instrument speed and apparatus type and utilizes this information to capture basic hydrodynamic effects on the dissolution rate.

You can add as many experimental phases as you want to better mimic the *in vivo* environment. This can be helpful when trying to design an *in vitro* dissolution method to achieve a meaningful ***in vitro-in vivo* correlation (IVIVC).**

Dissolution Media and Microclimate pH

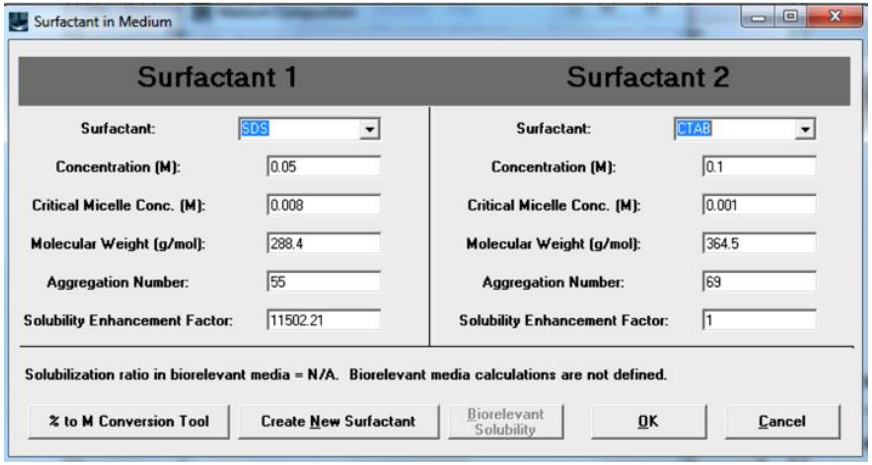
DDDPlus has a sophisticated pH engine to calculate the dissolution media pH and solubility of each ingredient at the surface and bulk pHs.
You can select from more than 90 built-in buffers, including all USP and biorelevant recipes, or easily design your own.
You can also vary the concentrations of the different ingredients to create custom buffers at various pH.

Microclimate pH

DDDPlus dynamically calculates the microclimate pH (pH at the diffusion layer of the particle) for each ingredient in the formulation. You can select either “microclimate pH” to calculate the solubility of the ingredient at the diffusion layer or “bulk pH” for solubility in the dissolution media. The “bulk pH” is utilized to capture any potential precipitation effects once the dissolved material reaches the bulk environment.

Surfactants

DDDPlus allows you to add up to 2 surfactants per dissolution media. You have the option to choose from a list of several common surfactants or create your own.



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Risk assessment of dissolution specifications

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Why *In Vitro* Dissolution?

- Common quality control tool
- Guides formulation development
- Dissolution has been recognized as surrogate for bioavailability
  - Some manufacturing changes can be approved using M&S and/or *in vitro* dissolution only
- Takes into consideration clinical impact of variations in **quality attributes** and **process parameters** ensuring consistent safety and efficacy profile

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Suarez Sharp, AAPS Annual Meeting 2012, Chicago, IL
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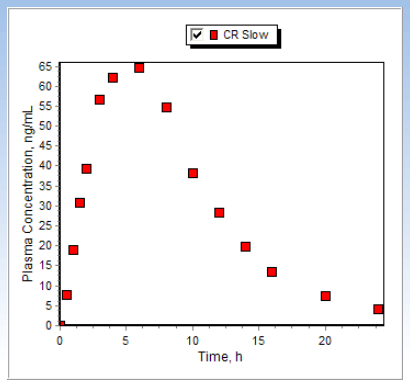
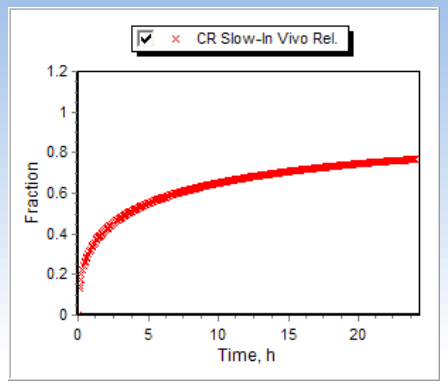
Developing a mechanistic in vitro-in vivo correlation (IVIVC)

Deconvolution
(with GastroPlus™ Mechanistic Absorption method)



Deconvolution



in vivo dissolution vs. time along the gut– **NOT F%!**

- Inputs (in addition to the data required for the traditional methods):
  - Physiological parameters
  - Drug properties (solubility, Peff, logP, pKa, 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

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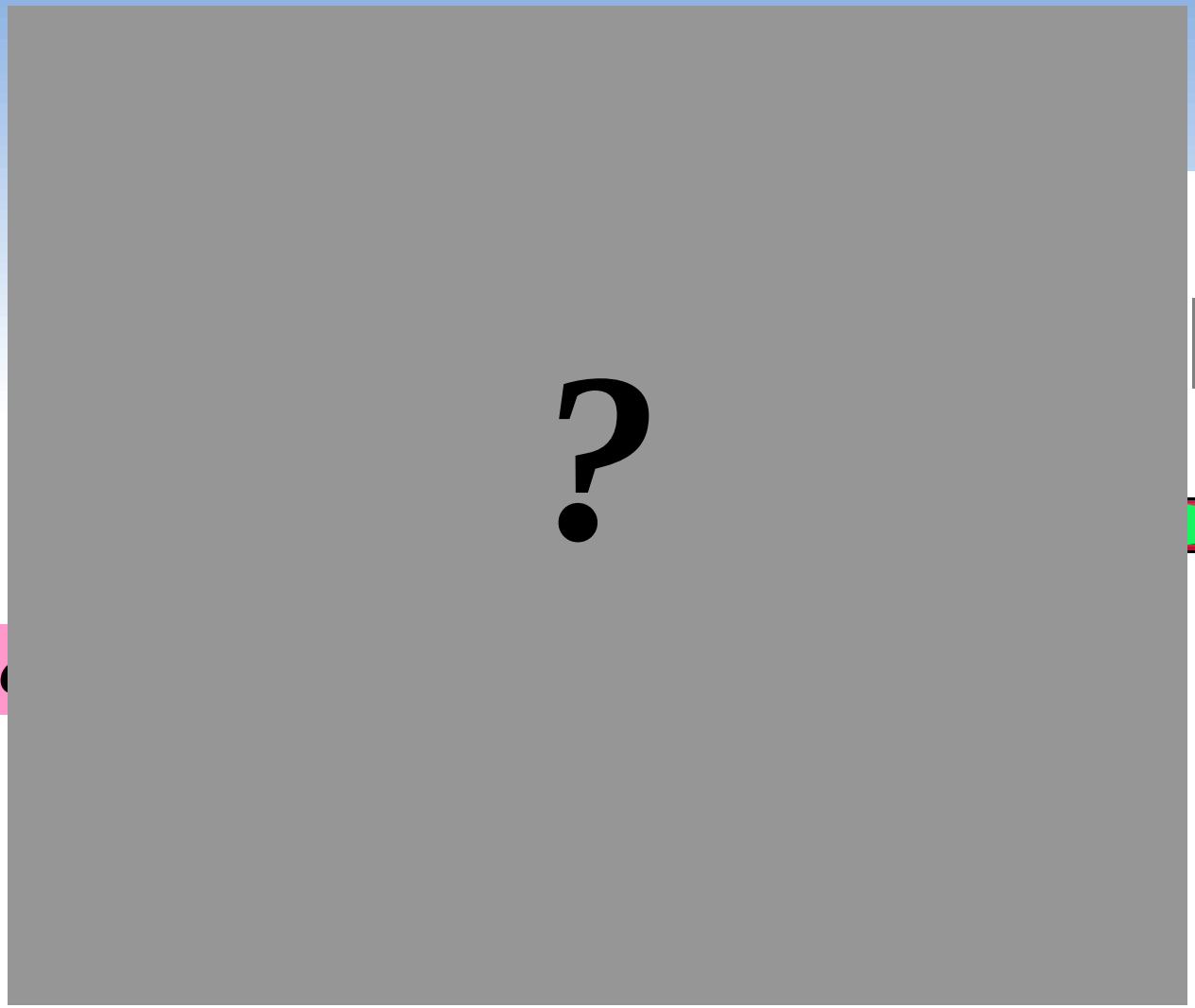
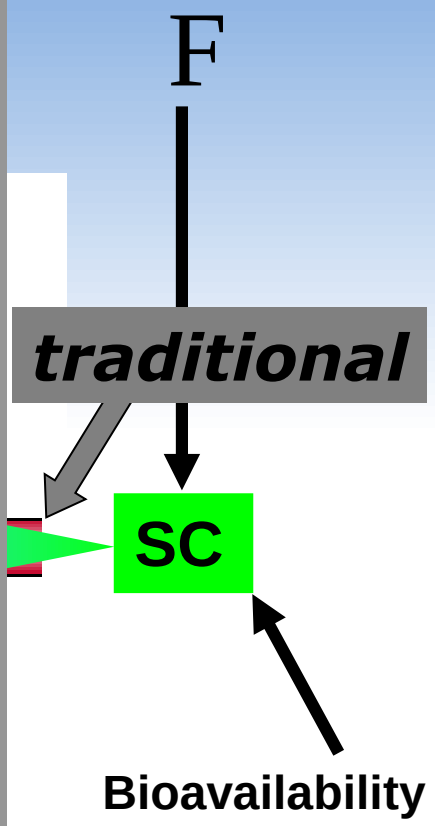
Difference between traditional and mechanistic deconvolution?





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

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Comparison of IVIVC Methods: Predicting PK of new products

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 • Yongsheng 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 using GatstroPlus™ simulation software.

Conclusions These observations indicate that an IVIVC model for a BCS class I drug may be applicable to varying formulations if the principle of the drug release is similar.

KEY WORDS BCS Class I drug · convolution · deconvolution · dissolution · IVIVC

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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

Table I Formulations Used for *In Vitro* and *In Vivo* Testing

Product	Strength of dosage for *in vitro* testing	Strength of dosage for *in vivo* testing
Reference extended release	25 mg, 100 mg[a], 200 mg	50 mg, 100 mg[a], 200 mg
Reference fast release	100 mg	100 mg
Test A	50 mg	50 mg
Test B	200 mg	200 mg
Test C	200 mg	200 mg
Test D	200 mg	200 mg
Test E	200 mg	200 mg

[a] Only used for external validation

Table III Physiochemical Properties of Drug Compound Used in Creating the Gastroplus IVIVC Model

Parameters	Values
Log P	1.9
Molecular weight	261.36 g
Ph off or reference solubility fully saturated solution	5.48
Concentration of fully saturated solution	16.9 mg/ml
Mean precipitation time	5 s
Diffusion. coefficient ($cm^2/s \times 10^5$)	0.74081
Drug particle density	1.2 g/ml
Particle size (diameter)	50 μm
Human jejunal permeability (Peff) ($cm/s \times 10^4$)	1.34

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Mirza et al., Pharm. Res. (2012)

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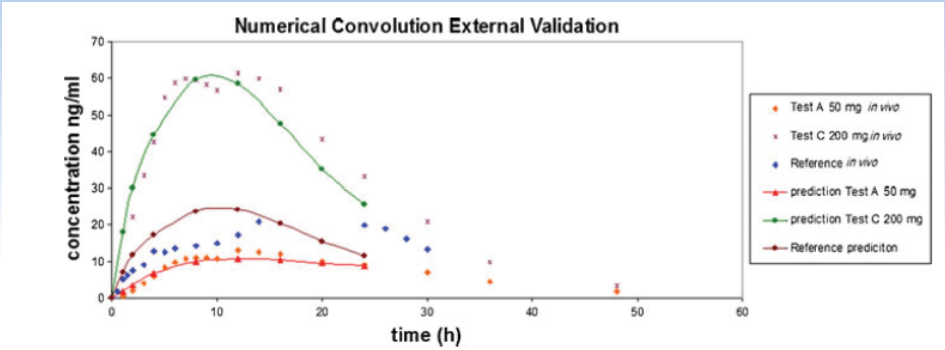
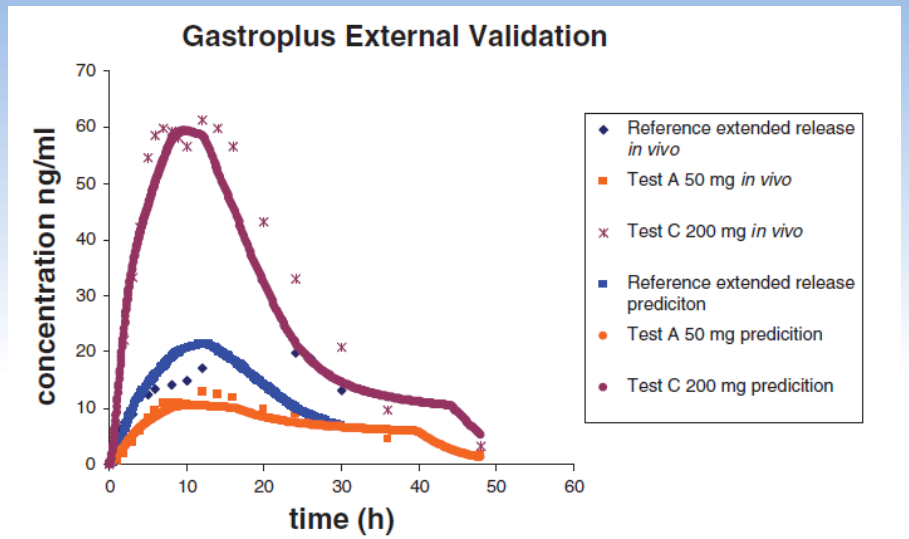
"External" Validation: Predicting PK of new products





Numerical Deconvolution

GastroPlus

- Internal validation of the IVIVC showed similar prediction accuracy
  - Internal validation = applying the same products used to build the IVIVC to test it
- GastroPlus showed "greater prediction accuracy" for the new products
  - External validation = predicting PK of new products with the IVIVC

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Mirza et al., Pharm. Res. (2012)

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IVIVC for BCS Class II (F = 66%)

AAPS PharmSciTech (© 2012)
DOI: 10.1208/s12249-012-9814-3

Research Article

Developing *In Vitro–In Vivo* Correlation of Risperidone Immediate Release Tablet

Yardi Saibi,[1,3] Hitoshi Sato,[1] and Hidehisa Tachiki[2]

Received 6 March 2012; accepted 30 May 2012

Abstract. The present study was aimed to predict the absorption profile of a risperidone immediate release tablet (IR) and to develop the level A *in vitro–in vivo* correlation (IVIVC) of the drug using the gastrointestinal simulation based on the advanced compartmental absorption and transit model implemented in GastroPlus™. Plasma concentration data, physicochemical, and pharmacokinetic properties of the drug were used in building its absorption profile in the gastrointestinal tract. Since the fraction absorbed of risperidone in simulation was more than 90% with low water solubility, the drug met the criteria of class II of the Biopharmaceutics Classification System. The IVIVC was developed based on the model built using the plasma data and the *in vitro* dissolution data in several dissolution media based on the Japanese Guideline for Bioequivalence Studies of Generic Products. The gastrointestinal absorption profile of risperidone was successfully predicted. A level A IVIVC was also successfully developed in all

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IVIVC for Risperidone IR Tablet

Table IV. Percent Prediction Error (PE) for Cmax and AUC of Reference Tablet

Observed values : Cmax=9.648 (ng/ml), AUC=57.83 (ng h/mL)

Dissolution Media	Cmax (ng/ml)	PE (%)	AUC (ng h/mL)	PE (%)
Phosphate buffer pH 4 (50 rpm)	10.28	−6.55	60.77	−5.08
Phosphate buffer pH 1.2 (50 rpm)	10.27	−6.45	60.77	−5.08
Phosphate buffer pH 6.8 (50 rpm)	9.94	−3.01	60.74	−5.03
Water	10.33	−7.07	60.77	−5.08
Phosphate buffer pH 6.8 (100 rpm)	9.51	1.41	60.70	−4.96

Table V. Percent Prediction Error (PE) for Cmax and AUC of Test Tablet

Observed values : Cmax=10.31 (ng/ml), AUC=62.80(ng h/mL)

Dissolution Media	Cmax (ng/ml)	PE (%)	AUC (ng/mL)	PE (%)
Phosphate buffer pH 4 (50 rpm)	10.26	0.48	60.77	3.23
Phosphate buffer pH 1.2 (50 rpm)	10.19	1.16	60.77	3.23
Phosphate buffer pH 6.8 (50 rpm)	10.09	2.13	60.75	3.26
Water	10.35	−0.39	60.77	3.23
Phosphate buffer pH 6.8 (100 rpm)	9.88	4.15	60.73	3.29

Re-engineered formulations and "virtual" bioequivalence: A successful biowaiver case study

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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?

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)

Formulation Specifications

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

Tistaert, C. AAPS 2015

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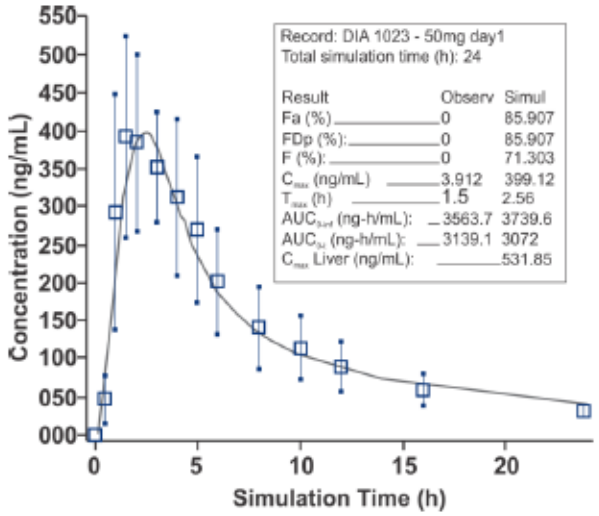
Part I: Model Validation

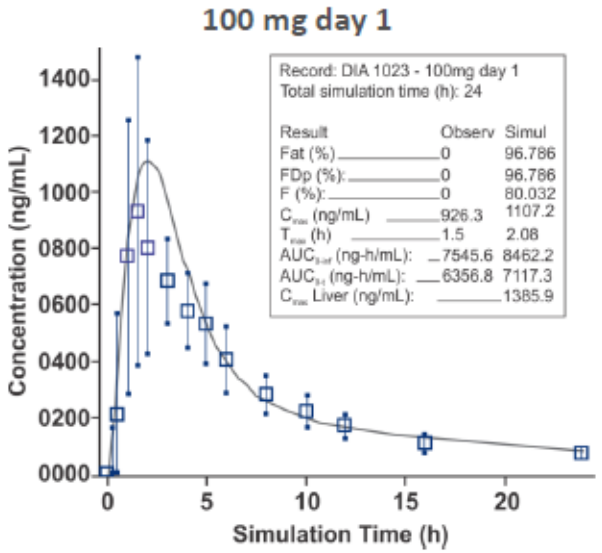
Model Validation

Simulated (lines) and experimental (points)

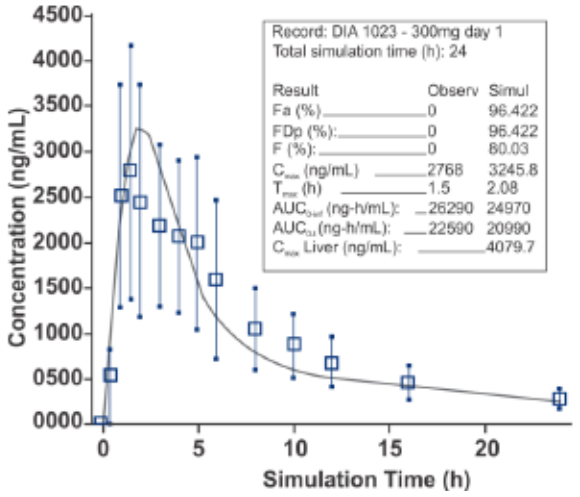
50 mg day 1



100 mg day 1



300 mg day 1



Excellent match between the measured and predicted Cp time profiles for 50, 100, and 300 mg doses

Cp-time: plasma concentration time

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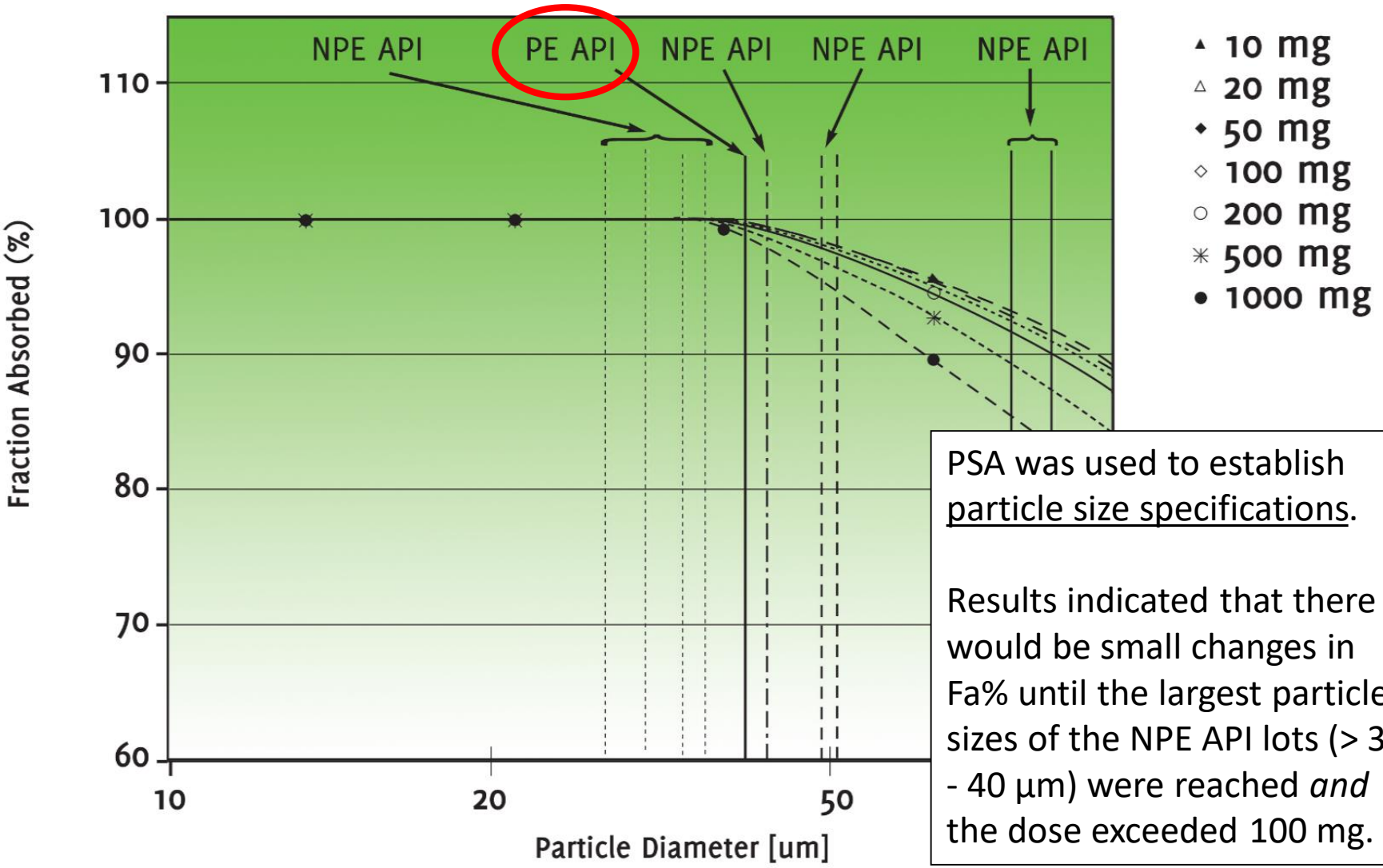
Part II: Parameter Sensitivity Analysis



PSA was used to establish <u>particle size specifications</u>.

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.

T_{max}: time to reach C_{max}

Particle Diameter [um]

Tistaert, C. AAPS 2015

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Part III: Virtual BE Simulations

Virtual Bioequivalence Study Simulations

- Using crossover virtual trial simulation comparing different formulations (PK parameters: C_{max} and AUC)

API Lot	NPE or PE	d10 (µm)	d50 (µm)	d90 (µm)
Lot 1	NPE	26	78	276
Lot 2	NPE	11	35	99
Lot 3	NPE	14	43	116
Lot 4	NPE	11	32	91
Lot 5	PE	17	41	88

API: active pharmaceutical ingredient; AUC_{∞}: area under the plasma concentration-time curve; C_{max}: maximum observed plasma concentration; 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; PK: pharmacokinetics

Tistaert, C. AAPS 2015

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Part III: Virtual BE Simulations

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

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

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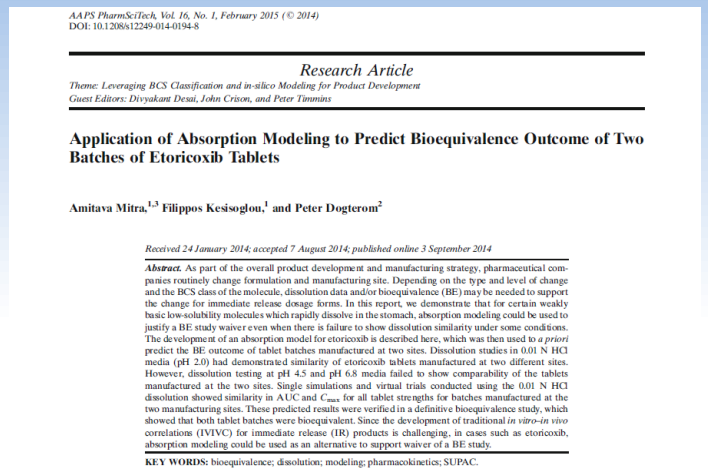
Summary

- 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
- Similarly there are other case studies of *Re-engineered formulations and a successful biowaiver*

Other recent examples: product changes & virtual BE

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



AAPS PharmSciTech, Vol. 16, No. 1, February 2015 (© 2014)
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

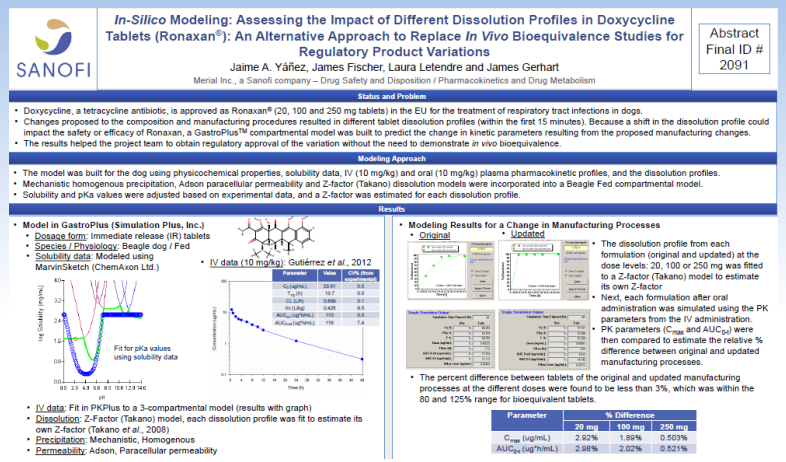
Amitava Mitra,[1,3] Filippos Kesisoglou,[1] and Peter Dogterom[2]

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 $AUC_{0\text{-}t}$) 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%
$AUC_{0\text{-}t}$ (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

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

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

Bin Yang[1], Chunnuan Wu[2], Bin Ji[3], Mingrui Wu[1], Zhonggui He[1], Lei Shang[4]* and Jin Sun[1,5]*

Affiliation:

[1]*Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, China;*

[2]*Department of Pharmacy, Tianjin Medical University Cancer Institute and Hospital, China;*

[3]*Department of Pharmaceutical analysis, School of Pharmacy, Shenyang Pharmaceutical University, China;*

[4]*School of Pharmacy, China Medical University, China;*

[5]*Municipal Key Laboratory of Biopharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, China;*

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

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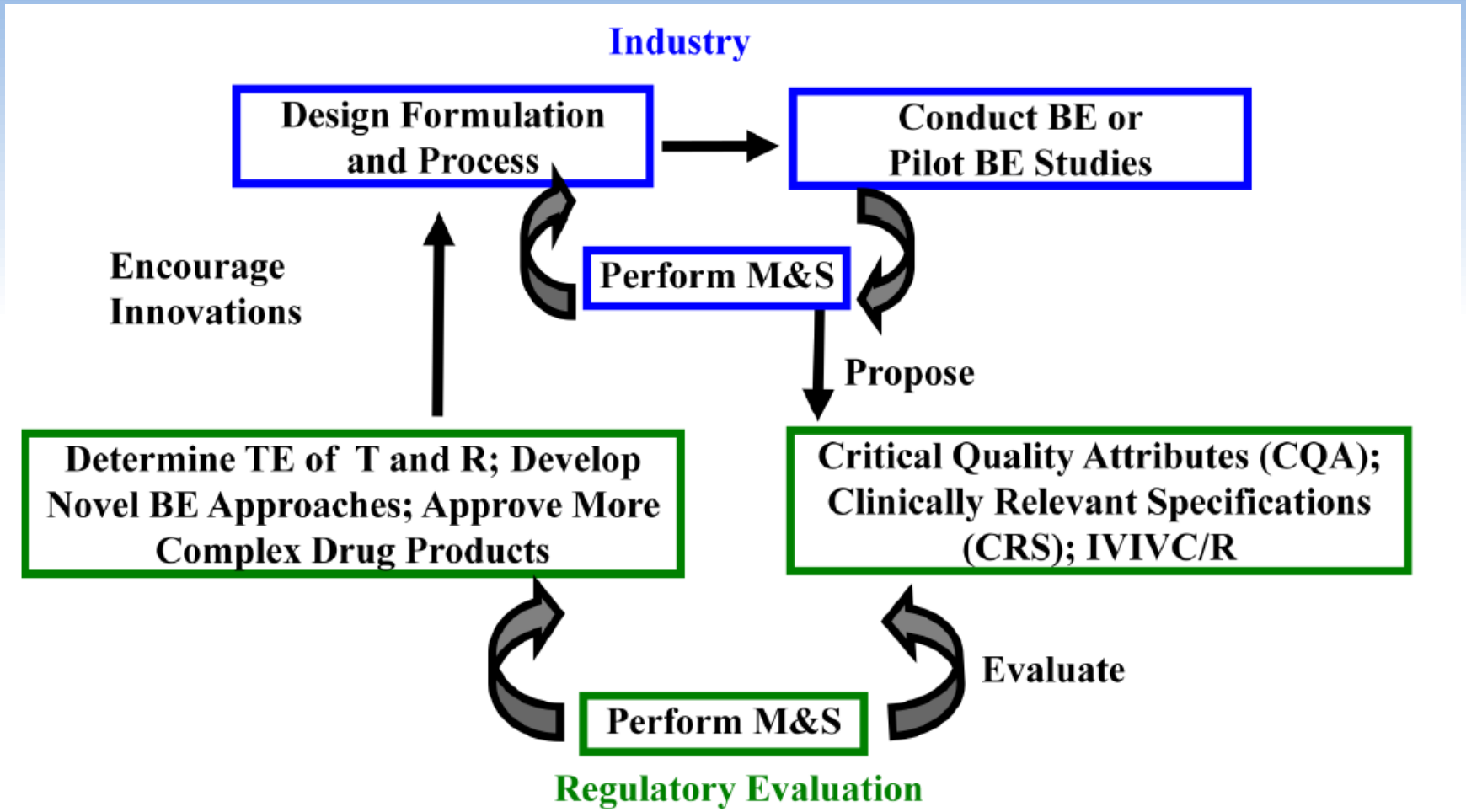
Future Directions

Innovation Model for Future ANDA



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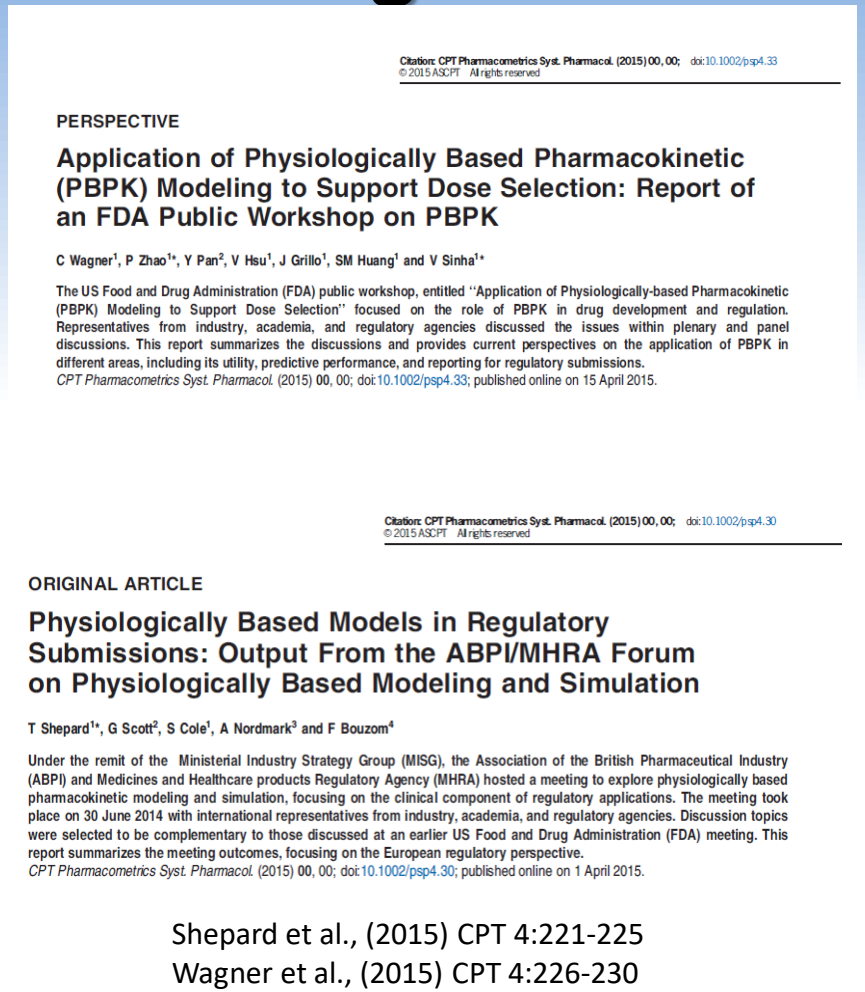
Advancing the Science – Together

- Open communication between regulatory agencies, pharmaceutical companies, universities, and software providers will help identify new M&S applications:
  - Food effect modeling
  - Disease state populations
  - Oral/non-oral delivery of drug products – virtual BE
- FDA is increasing funding to scientists **from across the world** to ensure that the regulatory review of new chemical entities (NCEs) and generic drugs is based on the best available science
  - Other regulatory agencies are also following suite

PBPK Modeling: Encouragement from Regulatory Agencies



Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.33

PERSPECTIVE

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*

The US Food and Drug Administration (FDA) public workshop, entitled ''Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection'' focused on the role of PBPK in drug development and regulation. Representatives from industry, academia, and regulatory agencies discussed the issues within plenary and panel discussions. This report summarizes the discussions and provides current perspectives on the application of PBPK in different areas, including its utility, predictive performance, and reporting for regulatory submissions.
CPT Pharmacometrics Syst. Pharmacol. (2015) **00**, 00; doi:10.1002/psp4.33; published online on 15 April 2015.

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.30

ORIGINAL ARTICLE

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

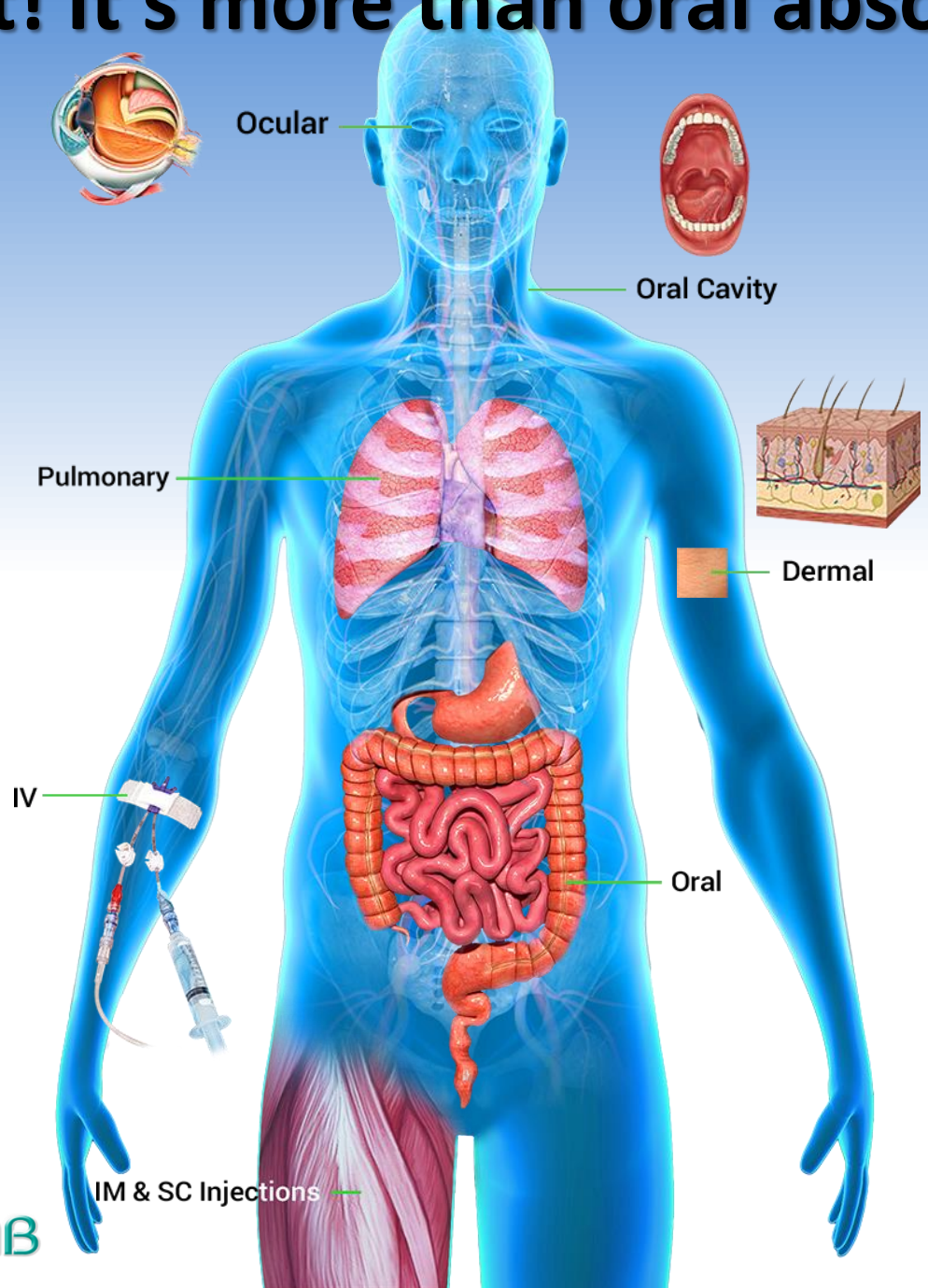
Under the remit of the Ministerial Industry Strategy Group (MISG), the Association of the British Pharmaceutical Industry (ABPI) and Medicines and Healthcare products Regulatory Agency (MHRA) hosted a meeting to explore physiologically based pharmacokinetic modeling and simulation, focusing on the clinical component of regulatory applications. The meeting took place on 30 June 2014 with international representatives from industry, academia, and regulatory agencies. Discussion topics were selected to be complementary to those discussed at an earlier US Food and Drug Administration (FDA) meeting. This report summarizes the meeting outcomes, focusing on the European regulatory perspective.
CPT Pharmacometrics Syst. Pharmacol. (2015) **00**, 00; doi:10.1002/psp4.30; published online on 1 April 2015.

Shepard et al., (2015) CPT 4:221-225
Wagner et al., (2015) CPT 4:226-230

- Both FDA and MHRA/EMA hosted PBPK workshops in 2014
- Discussed areas where PBPK modeling is helpful:
  - Dose selection & First-in-Human (FIH) predictions
  - Drug-drug interactions (DDIs)
  - Pediatric & special populations
  - Absorption/virtual bioequivalence
  - Food effects (not yet applicable)

5 yr Research Collaboration Agreement with the FDA (2014-19)

But wait! It's more than oral absorption…



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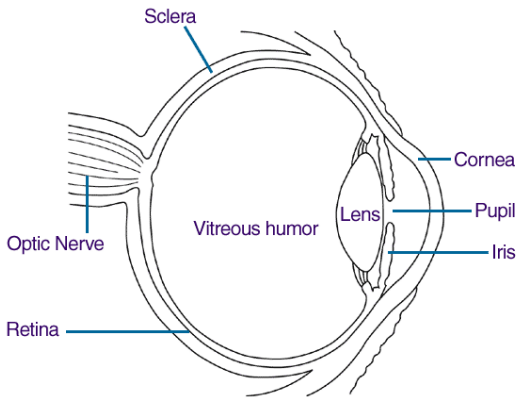
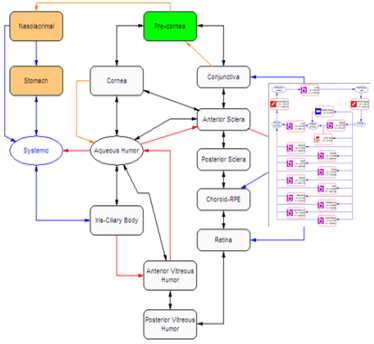
Cooperation Grant with the FDA (2014-16)

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





Cooperation Grant with the FDA (2015-17)

- 3-year ***funded*** collaborative project with the FDA Office of Generic Drugs on the development & validation of GastroPlus mechanistic models for **long-acting injectables**
- Consortium members: FDA, Amgen, Teva, Dr. Reddy's, GSK, Merck, and Novartis

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FDA Office of Generic Drugs: 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

rary.com). DOI 10.1002/jps.24474

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dels to test sensitivity of PK metrics to the changes in formulation variables.
is in the public domain in the USA J Pharm Sci
e; 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 factors (ASFs) by deconvo
validated for other PK pr
explored three key areas w
used to help identify optim
critical formulations variab
for the IR tablet that show
decreased. Finally, virtual t
Virtual bioequivalence stu
test may be a more sensitiv
predictive model is a poten

KEY WORDS: advanced
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 using GastroPlus™ simulation software.

Conclusions These observations indicate that an IVIVC model for a BCS class I drug may be applicable to varying formulations
f the principles of the drug release is similar.

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 correlation (IVIVC) has been defined by the
ites Pharmacopeia (USP) Subcommittee on Bio-
tics as "the establishment of a rational rela-
between a biological property, or parameter
m a biological property produced by a dosage
a physicochemical property or characteristic of
dosage form" (1). The Food and Drug Admin-
defines IVIVC as "A predictive mathematical
scribing the relationship between an *in vitro*
of an extended release dosage form (usually the
ent of drug dissolution or release) and a rele-
e response, e.g., plasma drug concentration or
drug absorbed" (2). In most cases, the *in vitro*
the rate or extent of drug dissolution or release
vivo response in the plasma drug concentration

Published online: 22 August 2012

Springer

Generating mechanistic IVIVCs to predict test formulations

(Mirza et al., 2012)

International Journal of Pharmaceutics 418 (2011) 151–160

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation☆

Wenlei Jiang, Stephanie Kim, Xinyuan Zhang, Robert A. Lionberger*, Barbara M. Davit, Dale P. Conner, Lawrence X. Yu

Office of Generic Drugs, Food and Drug Administration, United States

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Physiologically based modeling
Quality-by-design
Bioequivalence
In vitro–in vivo correlation
Drug development and review

ABSTRACT

Advances in predicting *in vivo* performance o
ucts are developed and reviewed. Modeling
drug product development and regulatory dr
the development of biorelevant specification
release products with rapid therapeutic onse
framework, and prediction of food effect. As
better application of biopharmaceutical mode
bioequivalence demonstration of complex dr
modeling and simulation approaches. A colla
in modeling and simulation will result in imp
public.

Published by Elsevier B.V.

Role of M&S in drug development and regulatory evaluation

(Jiang et al., 2011)

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GastroPlus™ User Group

Providing a global network for scientists to enhance the efficiency of discovery and development research through GastroPlus modeling and simulation

- In 2013, scientists from 17 companies in North America and Europe formed the GastroPlus User Group
- To date, >950 members on the LinkedIn group page – membership is free!

  http://www.linkedin.com/groups/GastroPlus-User-Group-5025927/about

Mission

Discuss best practices, Q&A and FAQs
Share knowledge of software functionality and applications
Present and advance M&S science via social media, webinars and face-to-face meetings
Establish pre-competitive areas of research and collaboration across industry and academia
Feed back improvements and software functionality requests to Simulations Plus
Advocate and promote enhanced adoption of M&S tools in drug discovery and development Understand and influence regulatory expectations for M&S submissions

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Thank you for your kind attention…