GastroPlus® PBBM/PBPK modeling: supporting R&D through regulatory interactions…

John DiBella
President, Lancaster Division
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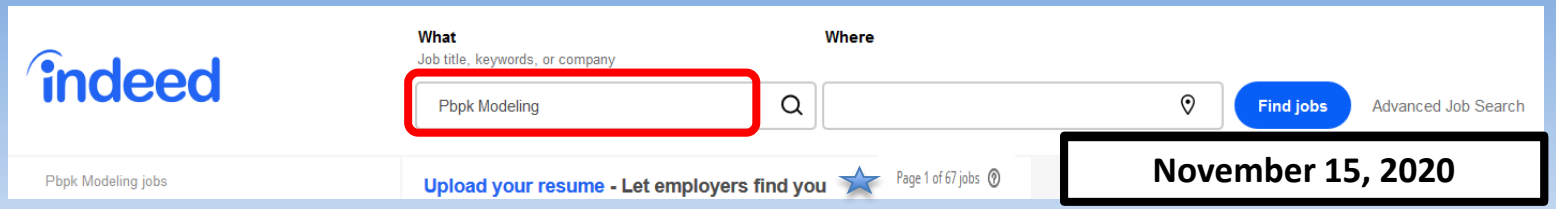
Evolving relationship between *in silico* tools and R&D

- **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" (current & future questions)**: How do I change the R&D process to reflect the availability of *in silico* tools and techniques?

What a great time to be a PBBM/PBPK modeler!



Director, Pharmacokinetics
Merck 4.1 ★
West Point, PA

- The candidate should be familiar with PK, PK/PD and PBPK modeling as tools to enable decision making.
- Experience in integrating preclinical ADME, PK, and...

20 days ago · Save job · More...

Director, Clinical Pharmacology and Pharmacometrics
Exelixis Inc. 3.6 ★
Alameda, CA

- Expertise in pre- and clinical pharmacology, hands-on modeling and simulation skills using NONMEM, R and/or other modeling and simulation software.

30+ days ago · Save job · More...

Scientist/Sr. Scientist PK/PD
Fusion Pharmaceuticals
Boston, MA

Easily apply

- Experience with PBPK modeling and/or disease and systems biology modeling a plus.
- Experience with PBPK modeling, population PK, and mechanistic PK/PD modeling...

25 days ago · Save job · More...

Scientist II | Sr. Scientist – Simulation Studies
Simulations Plus, Inc.
Lancaster, CA 93534

- Experience should include performing PBPK modeling of distribution of compounds in animals and humans.
- Use mechanistic, physiologically-based pharmacokinetic ...

30+ days ago · Save job · More...

Scientist, Director PKPD Modeling
Gossamer Bio
San Diego, CA 92121 (Torrey Pines area)

- Publication record highlighting application of original PK-PD modeling strategies to guide advancement of drug candidates from discovery through early clinical...

30+ days ago · Save job · More...

Senior Research Scientist - Metabolism and Toxicokinetics
Corteva Agriscience 3.8 ★
Newark, DE 19711

- Experience using commercial pharmacokinetic and PBPK modeling software (e.g. Phoenix® WinNonlin®, GastroPlus®).

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FELLOW - POST DOC - RESEARCH
Children's Hospital Los Angeles 4.1 ★
Los Angeles, CA 90029 (Hollywood area)

- Prior experience with PBPK and/or population modeling.
- Working with physicians, clinical pharmacists, and other engineers to learn and use laboratory software...

30+ days ago · Save job · More...

Postdoctoral Associate
Rutgers University 4.2 ★
New Brunswick, NJ

- Strong background in pharmacokinetics and modeling is required.
- Department of Pharmaceutics (Dr. Leonid Kagan Laboratory) invites applications for a...

19 days ago · Save job · More...

system one

Clinical Pharmacology Scientist (Associate Director)
System One 3.6 ★
Florham Park, NJ

- Working knowledge of PBPK and PK/PD modeling and simulation software packages such as GastroPlus, SimCYP, NONMEM, PDxPop, R.

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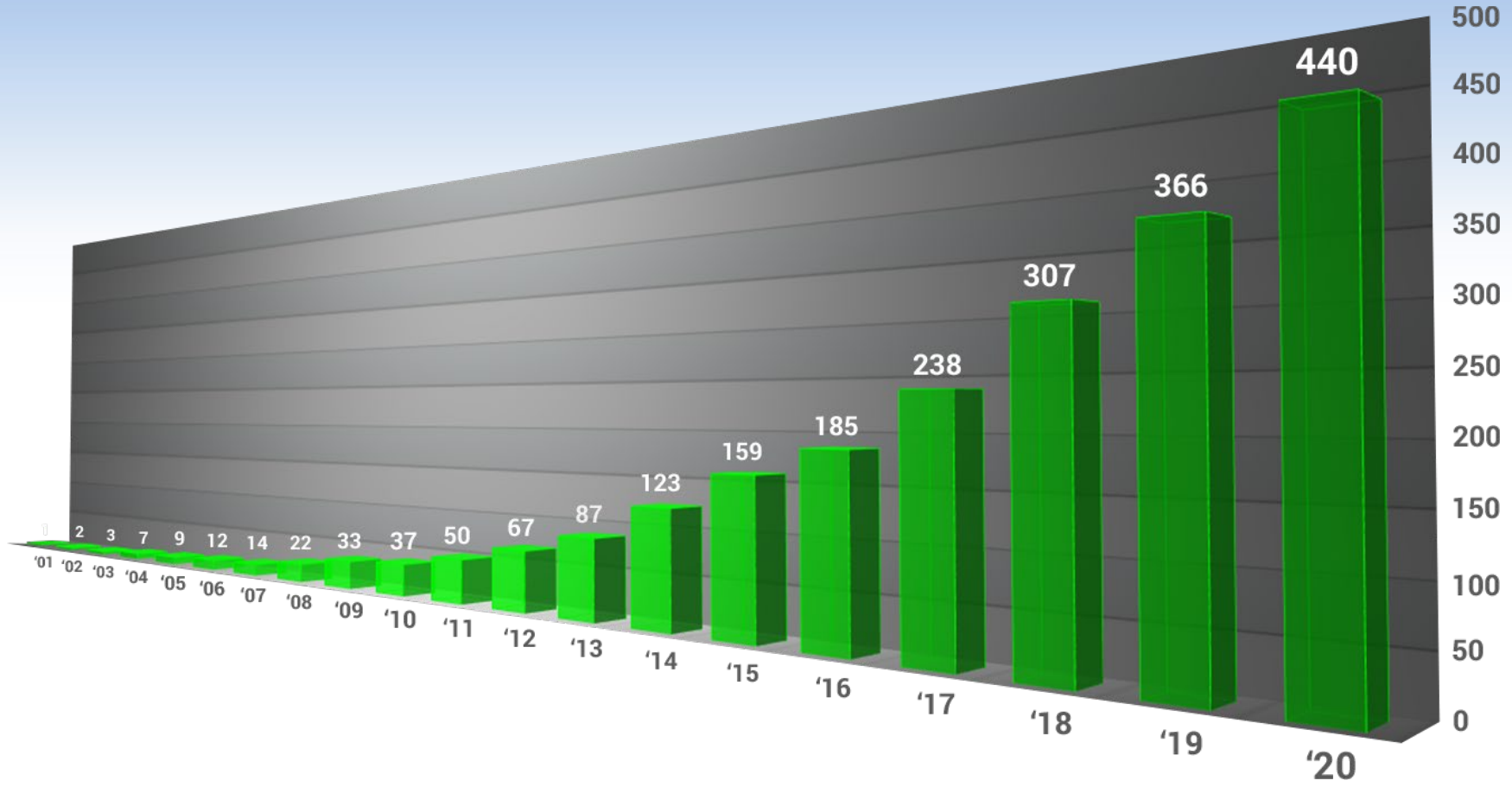
Peer-reviewed publications citing GastroPlus applications



[Simulations Plus Resource Center]

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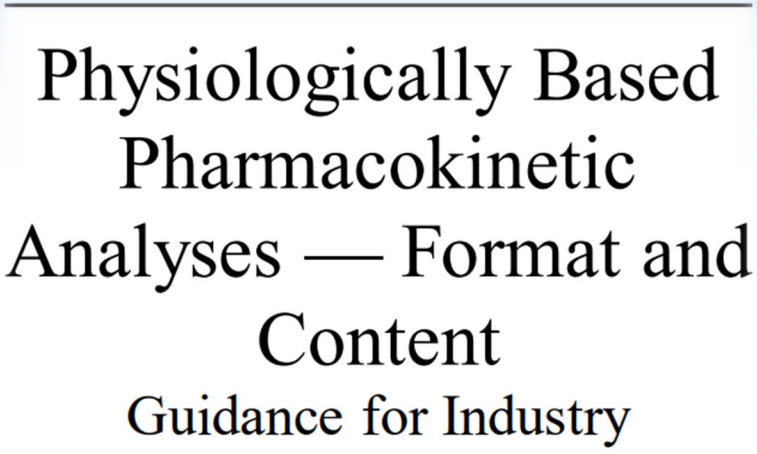
The regulatory push…

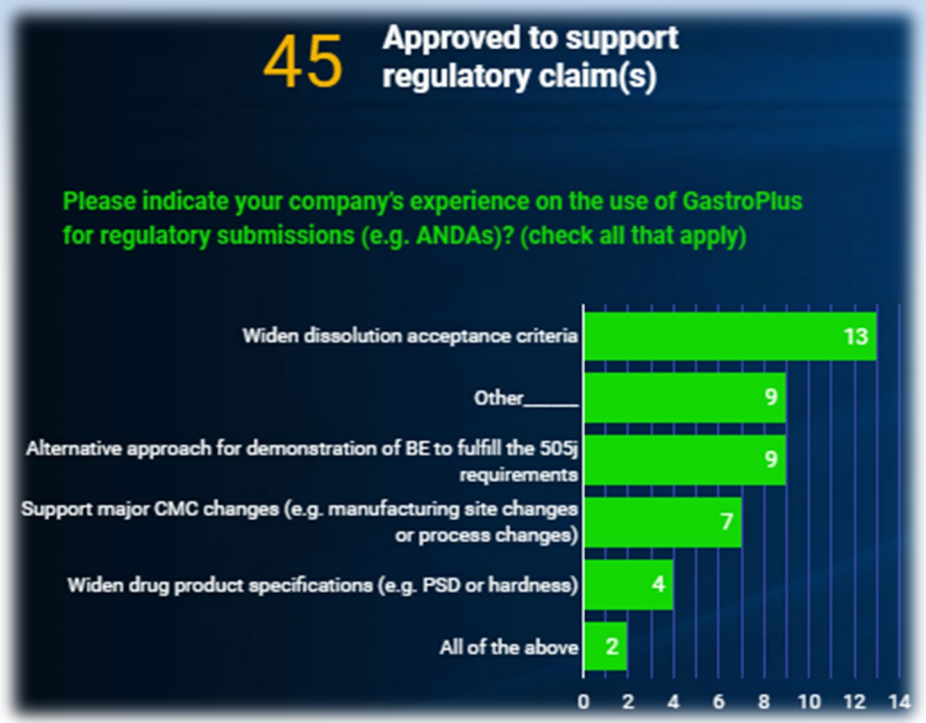


https://www.fda.gov/media/101469/download

- ALECENSA® (**absorption/PPI DDI**)
- BRAFTOVI® (**metabolism DDI**)
- CALQUENCE® (**particle size specs**)
- FARYDAK® (**food effect/PPI predictions**)
- INLYTA® (**transporter DDI**)
- MEKINIST® (**transporter DDI**)
- MEKTOVI® (**metabolism DDI**)
- OPSUMIT® (**particle size specs**)
- TAMIFLU® (**pediatric dose selection**)
- ZURAMPIC® (**wider product specs**)
- … and more!

2020 generic drug company survey

- Surveyed >30 generic drug companies licensing GastroPlus and/or working with our consulting teams
- Invited responses to:
  - Guide GastroPlus R&D activities heading into 2021
  - Describe use cases and regulatory interactions with GastroPlus
- Several questions included:
  - Which **new formulation type** would you find most useful in GastroPlus?
  - Which **new population group** would you find most useful to assist with virtual BE trials in GastroPlus?



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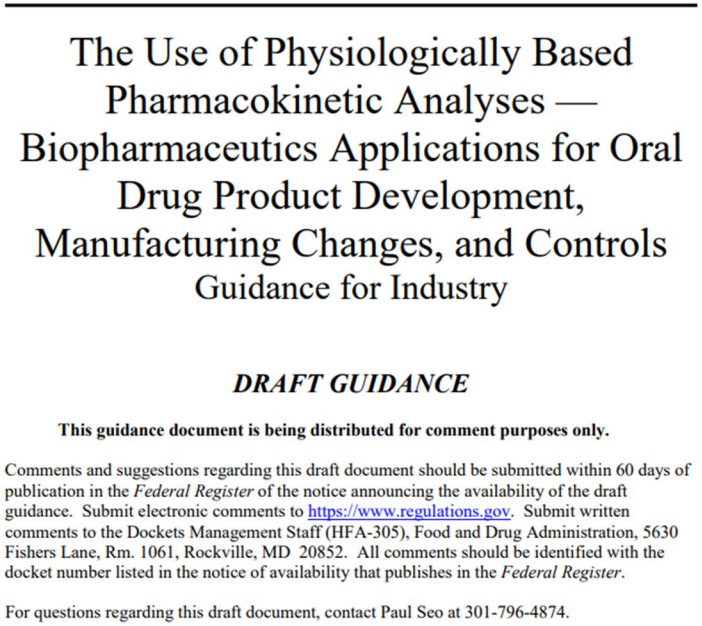
PBBM/PBPK modeling to support regulatory interactions: New guidance documents!



The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls
Guidance for Industry

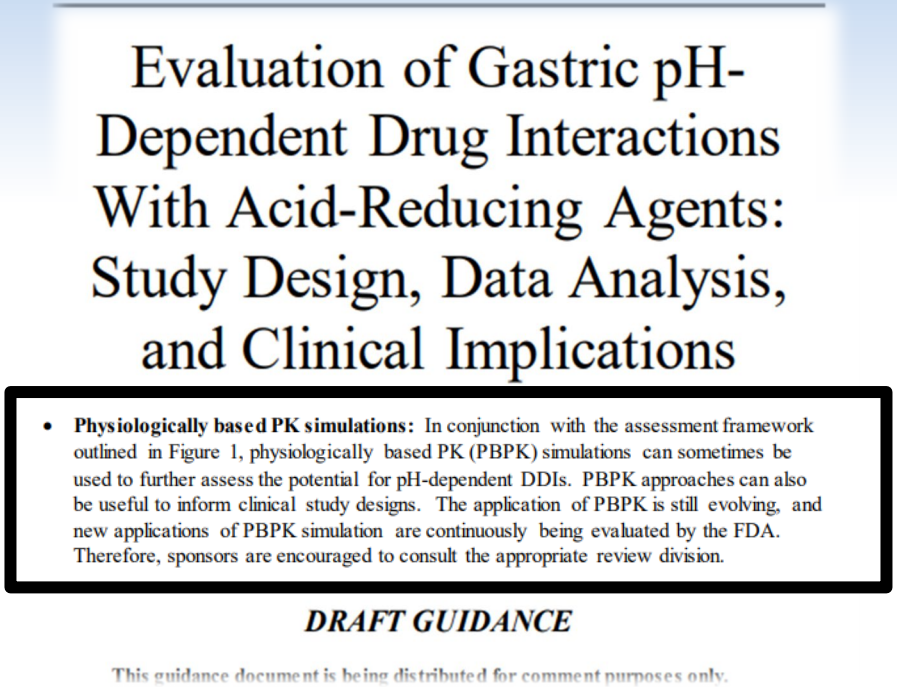
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Paul Seo at 301-796-4874.

https://www.fda.gov/media/142500/download



Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

- **Physiologically based PK simulations:** In conjunction with the assessment framework outlined in Figure 1, physiologically based PK (PBPK) simulations can sometimes be used to further assess the potential for pH-dependent DDIs. PBPK approaches can also be useful to inform clinical study designs. The application of PBPK is still evolving, and new applications of PBPK simulation are continuously being evaluated by the FDA. Therefore, sponsors are encouraged to consult the appropriate review division.

DRAFT GUIDANCE

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https://www.fda.gov/media/144026/download

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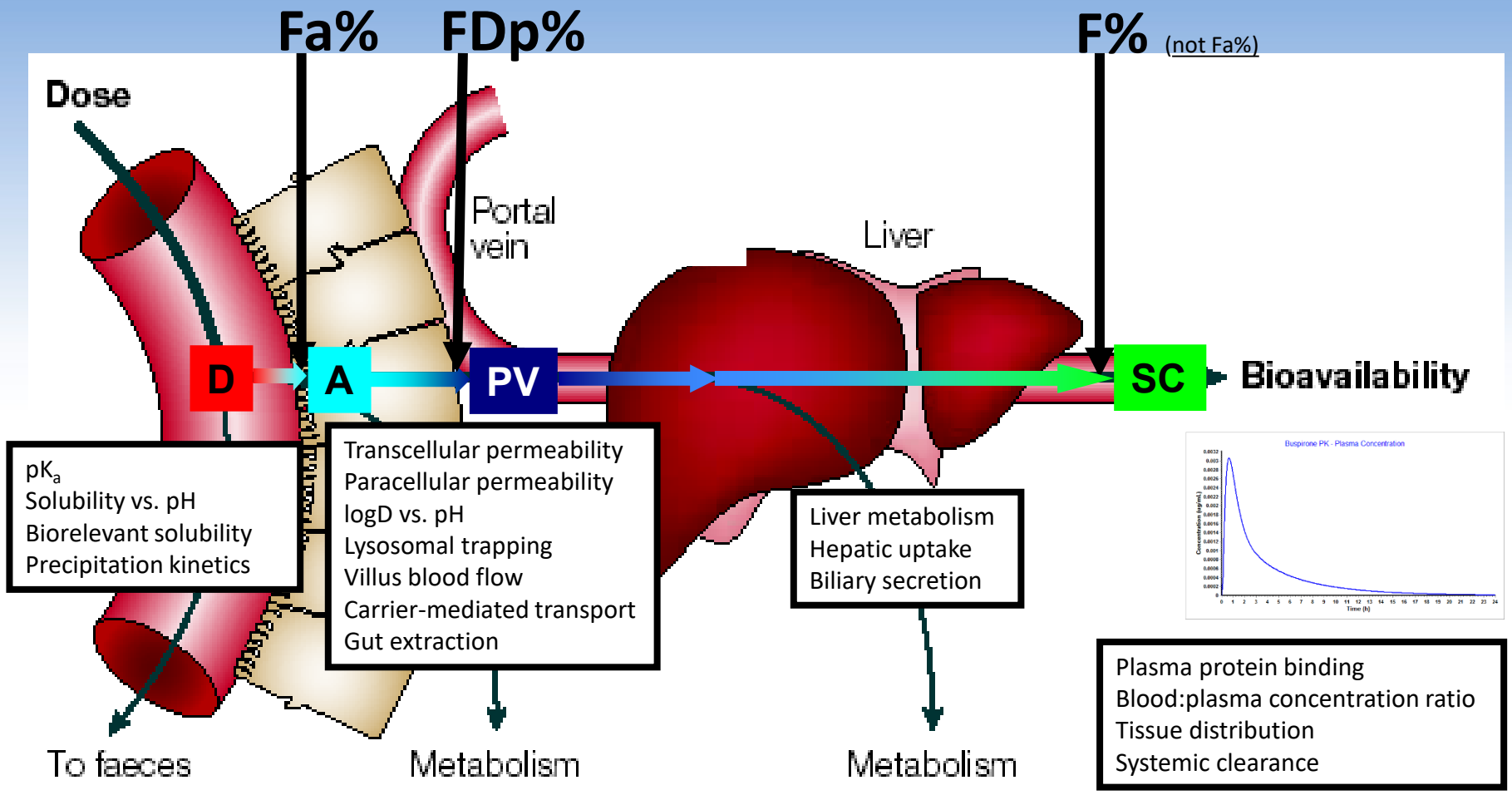
Outline

- How is GastroPlus® structured?
- How is GastroPlus® applied to support oral product development?
- Conclusions

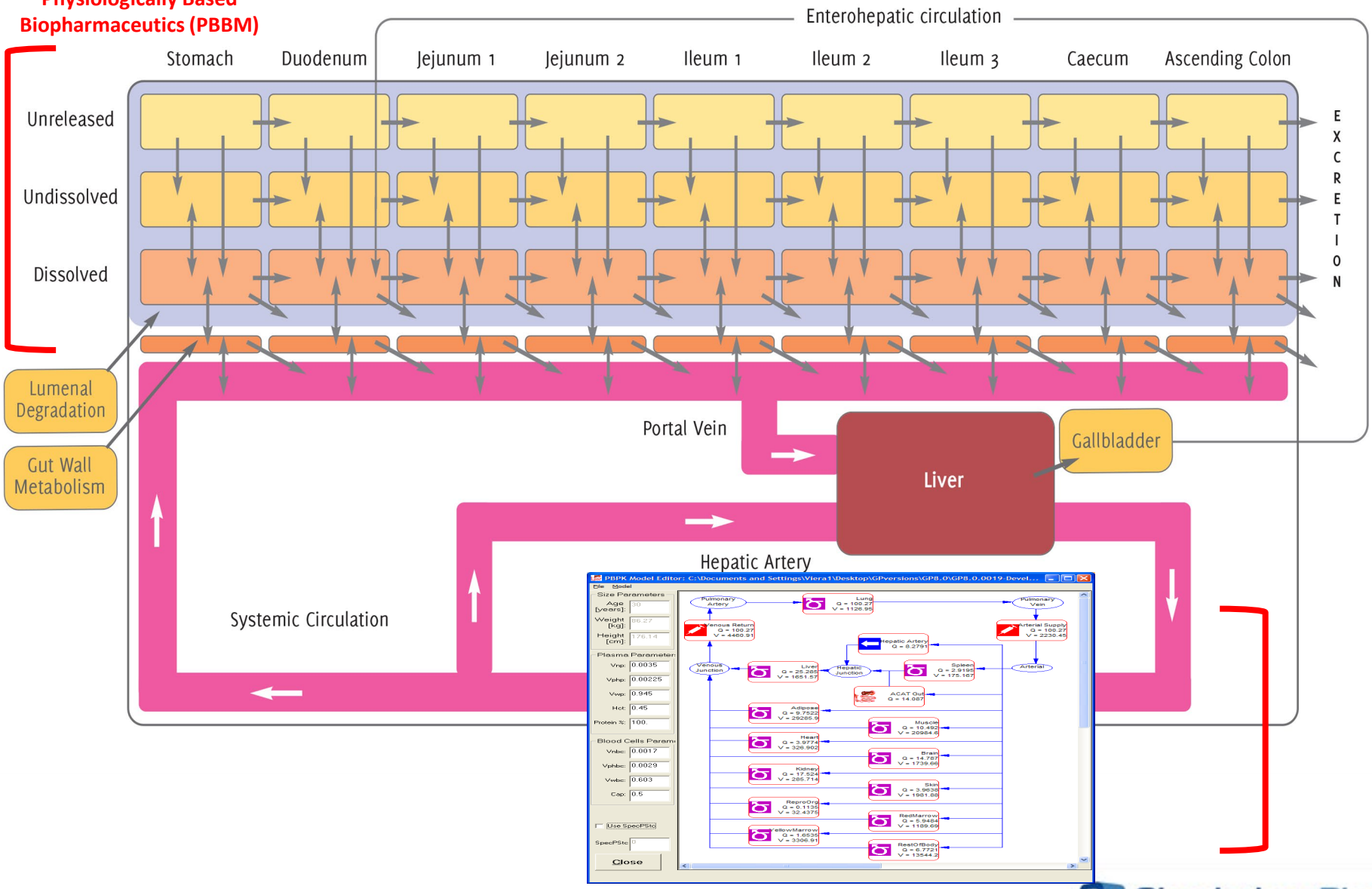
What's happening *in vivo*?



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

Advanced Compartmental Absorption and Transit Model (ACAT™)

Physiologically Based Biopharmaceutics (PBBM)



Physiologically Based Pharmacokinetics (PBPK)

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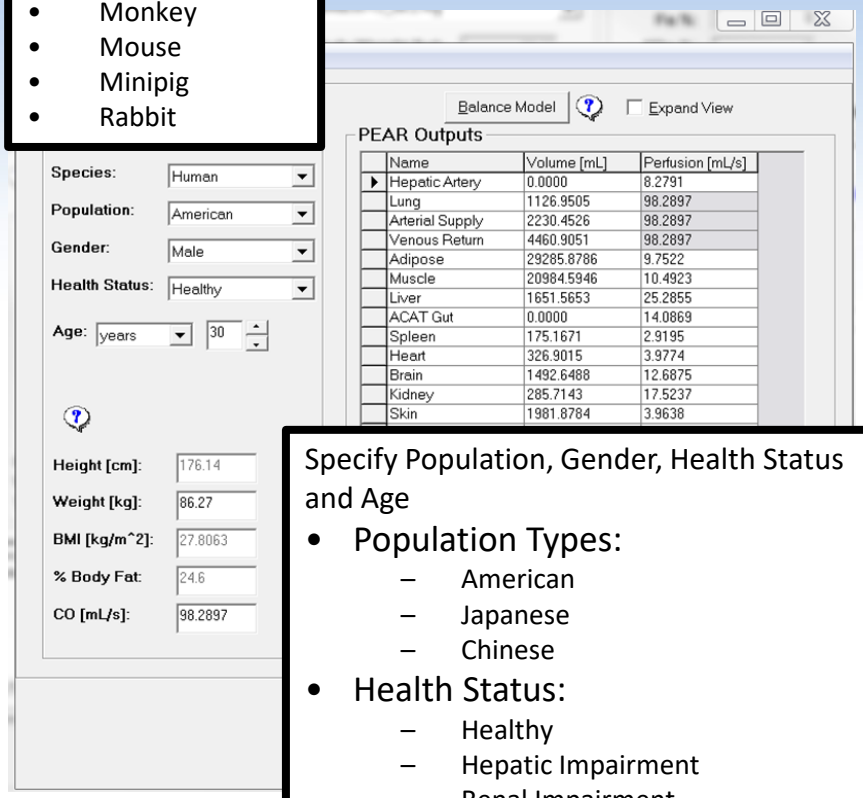
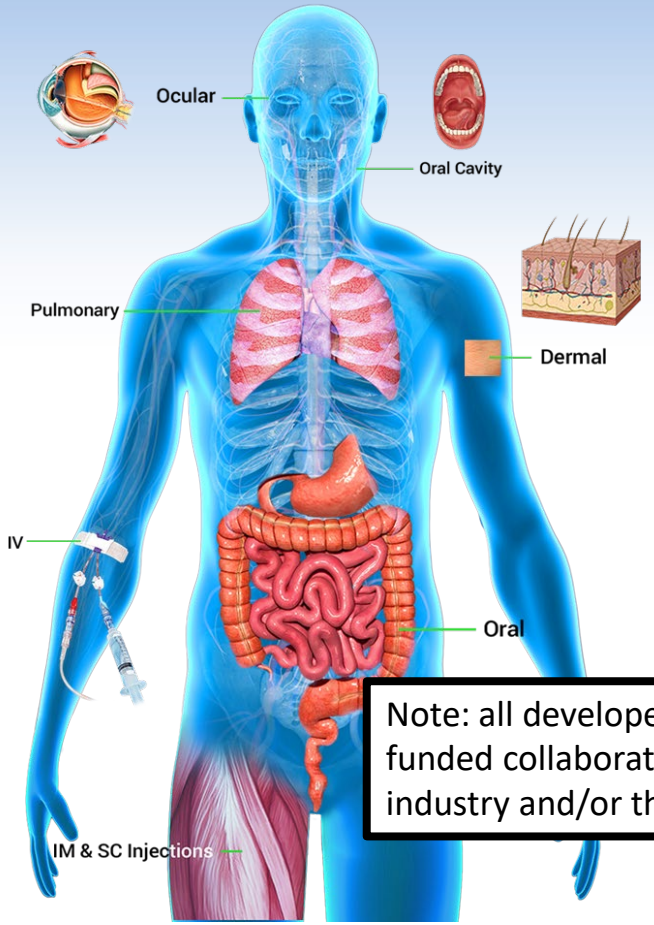
Validated system models in GastroPlus®

Select Species:
- Human
- Rat
- Dog
- Monkey
- Mouse
- Minipig
- Rabbit



Name	Volume [mL]	Perfusion [mL/s]
Hepatic Artery	0.0000	8.2791
Lung	1126.9505	98.2897
Arterial Supply	2230.4526	98.2897
Venous Return	4460.9051	98.2897
Adipose	29285.8786	9.7522
Muscle	20984.5946	10.4923
Liver	1651.5653	25.2855
ACAT Gut	0.0000	14.0869
Spleen	175.1671	2.9195
Heart	326.9015	3.9774
Brain	1492.6488	12.6875
Kidney	285.7143	17.5237
Skin	1981.8784	3.9638

Specify Population, Gender, Health Status and Age
- Population Types:
  - American
  - Japanese
  - Chinese
- Health Status:
  - Healthy
  - Hepatic Impairment
  - Renal Impairment
  - Obesity
  - Pregnancy
- Age:
  - Day 1 of birth (16 weeks premature) -> 85 years old



Note: all developed through funded collaborations with industry and/or the U.S. FDA

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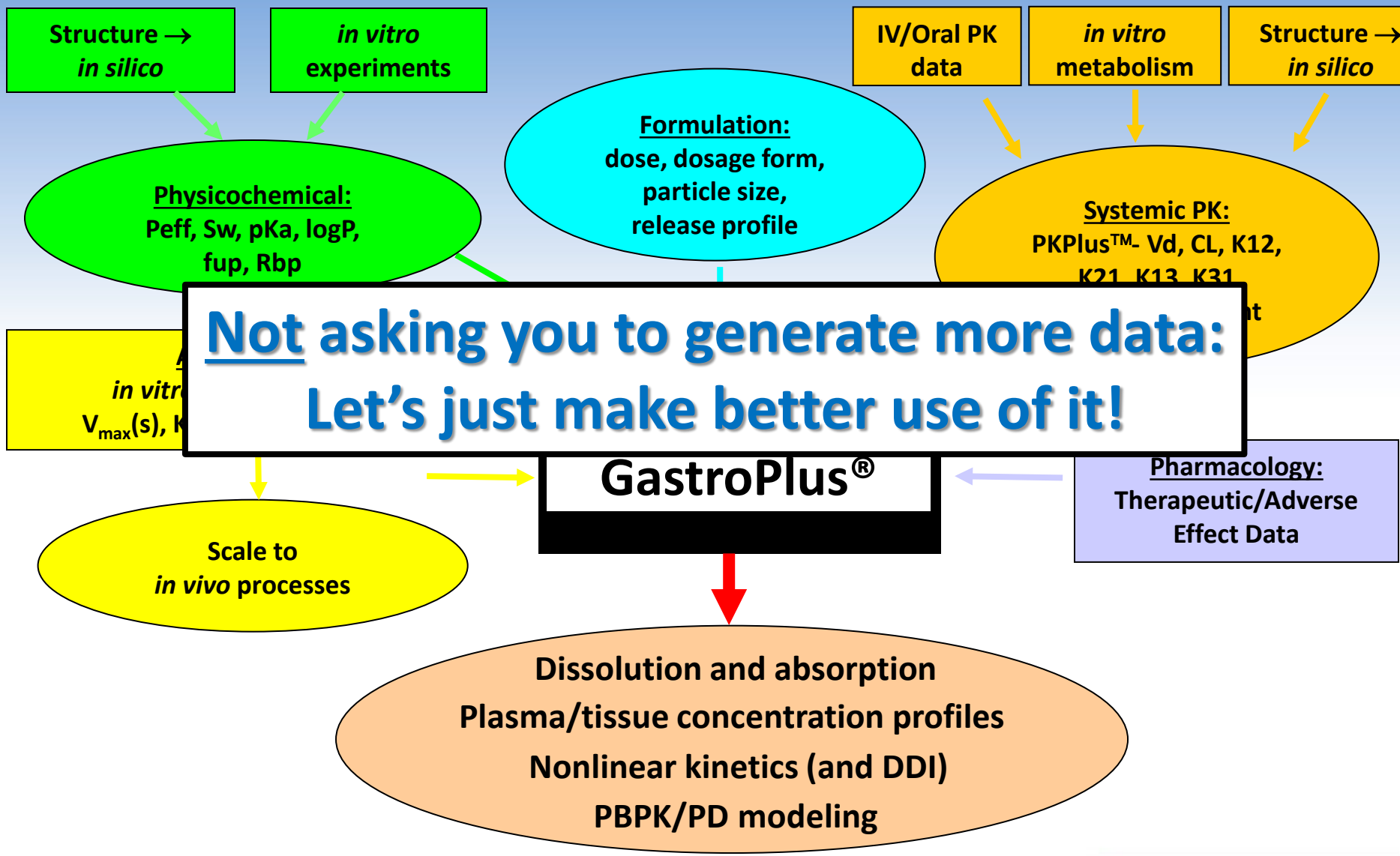
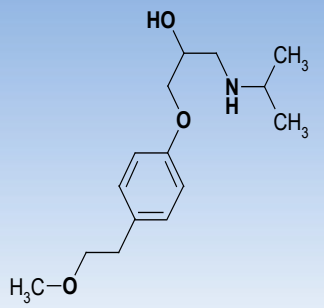
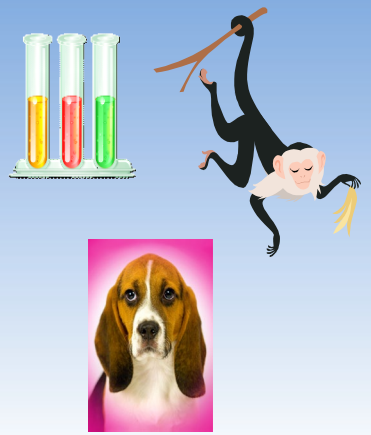
The Big Picture – small molecule inputs



Discovery | Preclinical | Clinical





Discovery PK

Combine *in silico* technologies to screen compound libraries in animals or humans

Incorporate preclinical/*in vitro* data to extend FIH simulations to full *in vivo* outcomes (IVIVE)

Identify toxic dose levels in preclinical species

Clinical PK/Pharmacology

Simulate population behaviors (e.g., pediatrics, disease)

Build PBPK-PD models

Predict DDIs

Pharmaceutical Development

Assess various strategies during formulation development

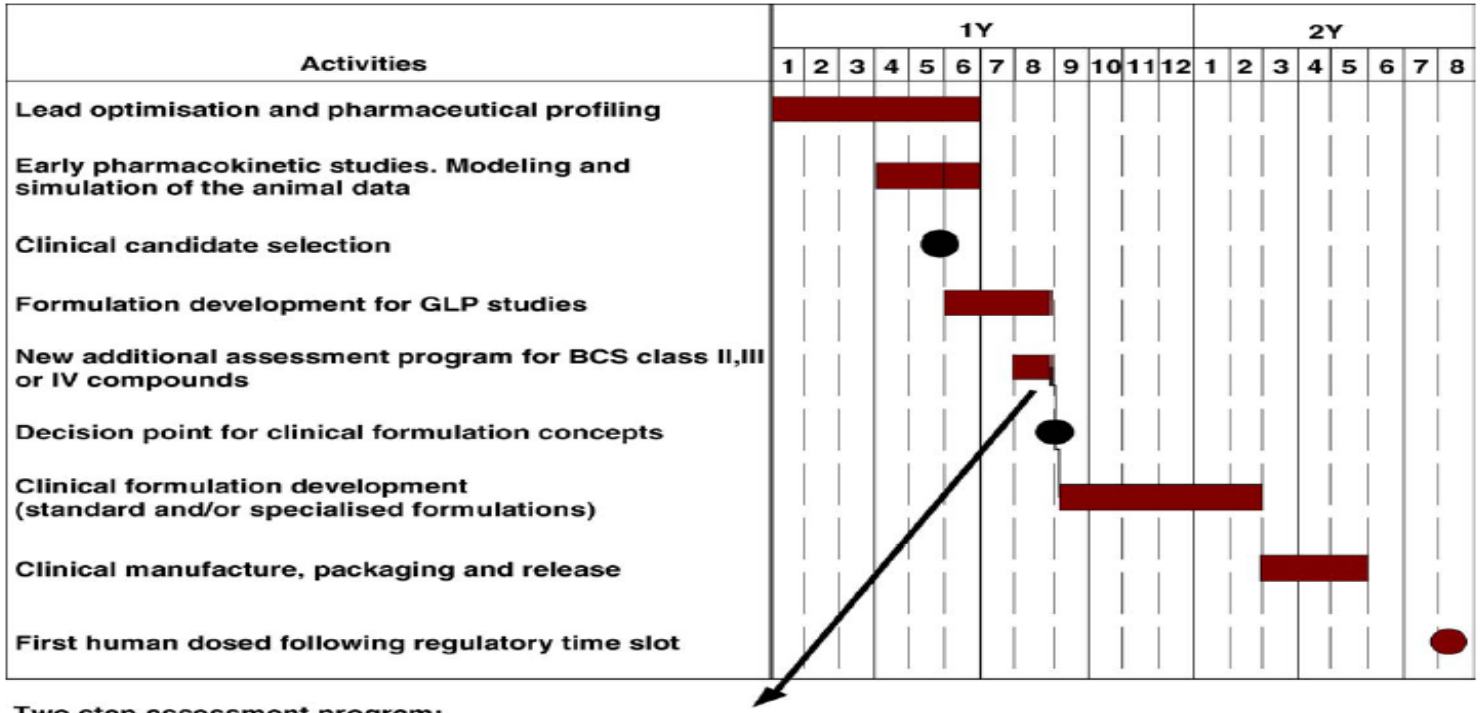
Assist with Quality by Design (QbD) implementation

Develop mechanistic *in vitro-in vivo* correlations (IVIVCs)

Understand food effects

Biopharmaceutical risk assessment program

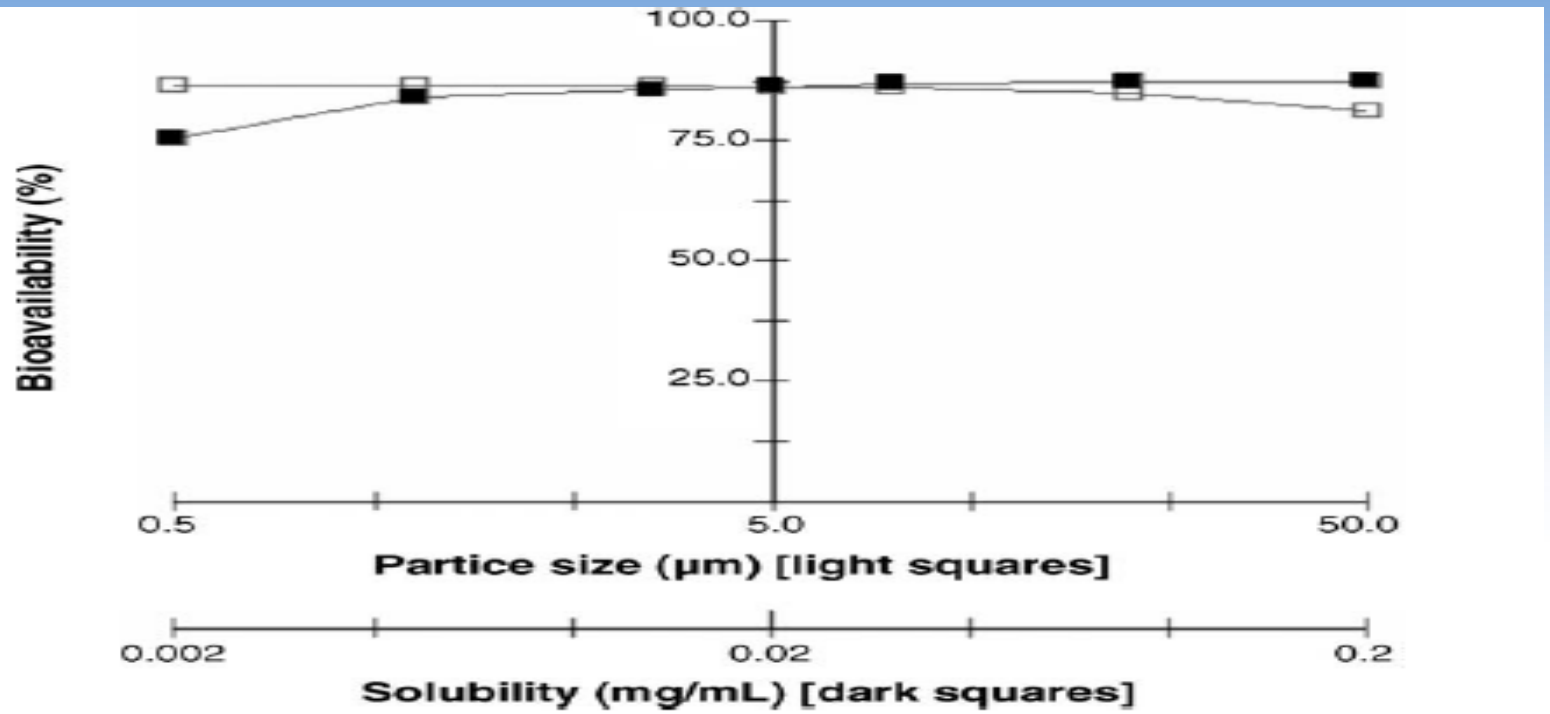
Pharmaceutical risk assessment strategy



- Critical parameters for a formulation can be identified before starting any *in vivo* work
  - Sensitivity analysis helps guide resource placement
- Assist with Quality by Design (QbD) implementation

Kuentz et al. Eur. J. Pharm. Sci. 2006. 27:91-99.

R1315 PSA for particle size and solubility



- 12 total simulations were run to assess the sensitivity of bioavailability to changes to particle size and solubility
  - 0.5 um ≤ particle size ≤ 50 um
  - 0.002 mg/ml ≤ solubility ≤ 0.2 mg/ml
- Results indicate that particle size reduction or solubility enhancement by technological means may not lead to improved absorption or higher bioavailability

Kuentz et al. Eur. J. Pharm. Sci. 2006. 27:91-99.

Comparison of simulated results with measured data for R1315

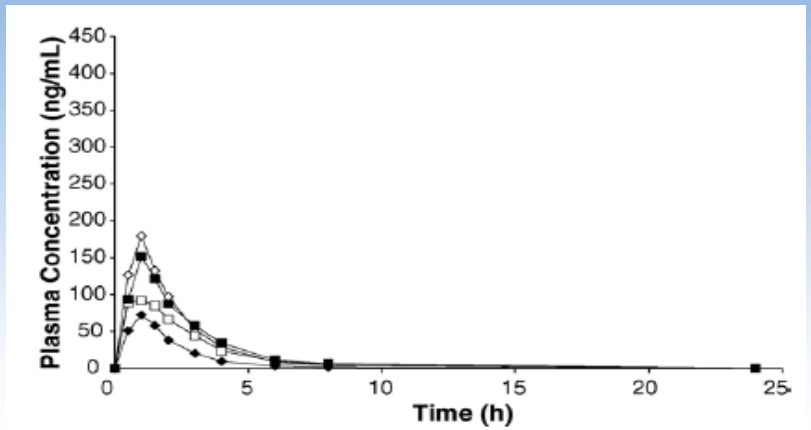


Fig. 7 – Plasma levels of individual dogs that received a solution. Diamonds hold for profiles of 2 mg/kg dose, whereas those of the 4 mg/kg dose are represented by squares. The light symbols hold for the fasted condition and the bold symbols for fed dogs.

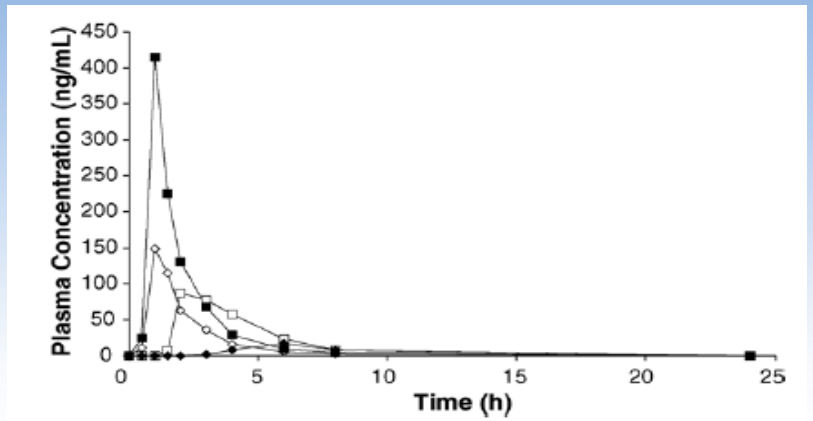


Fig. 8 – Plasma levels of individual dogs that received a capsule. Diamonds hold for profiles of 2 mg/kg dose, whereas those of the 4 mg/kg dose are represented by squares. The light symbols hold for the fasted condition and the bold symbols for fed dogs.

- Based upon the predictions from GastroPlus™, *in vivo* dog studies were performed using two different formulations
  - "Best" formulation: Cremophor vehicle solution
  - "Worst" formulation: Pure drug substance in capsule
- While the variability is high, there is no significant difference in AUC between the two formulations

Kuentz et al. Eur. J. Pharm. Sci. 2006. 27:91-99.

Biorelevant dissolution to guide formulation switch

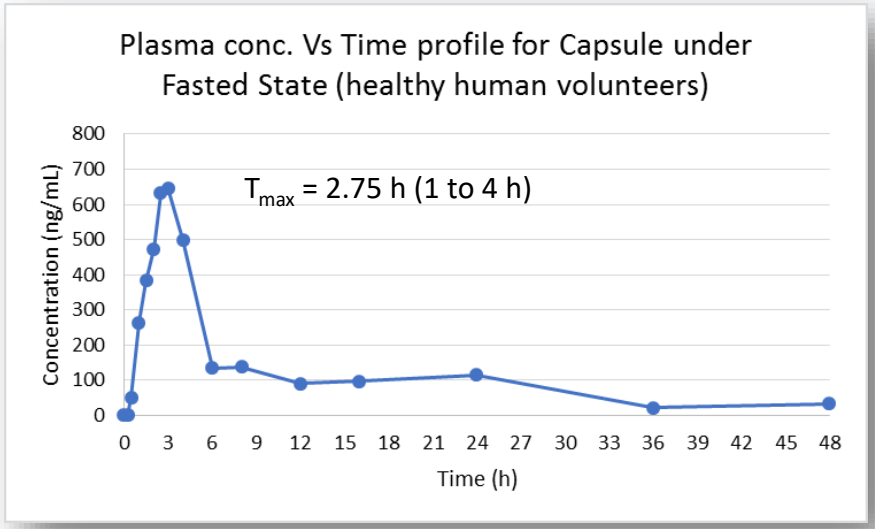
Formulation switch for a NCE

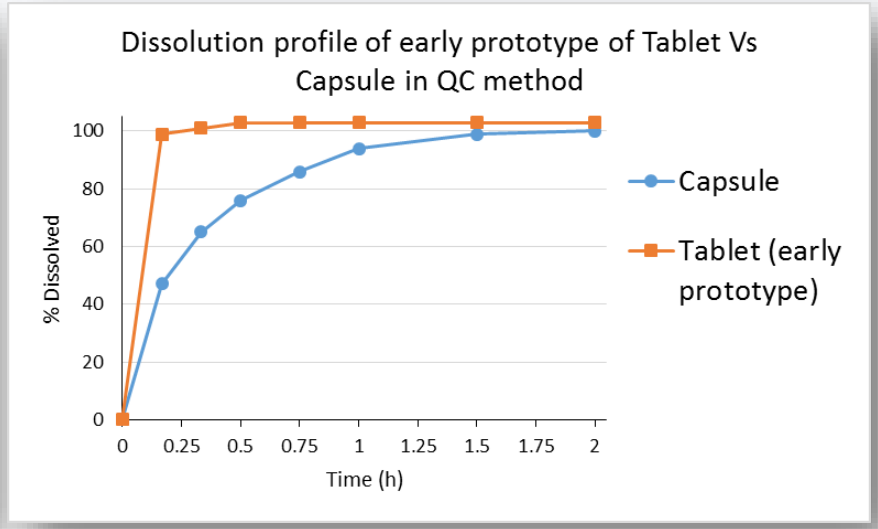
- BCS Class II compound from Sun Pharmaceuticals:
  - Practically insoluble in water
  - pKa: Base = 2.66, Acid1 = 9.02, Acid2 = 9.73
  - Log D: 3.27 @ pH 7.45
  - Permeability (Caco-2): 3.5×10^{-6} cm/sec
- **Product design:** Enabling formulation for improved solubility and oral bioavailability
- **Study objective:** Identify a biorelevant dissolution condition for screening formulations for formulation switch

Ketkar A. SPDS 6th International Annual Symposium on Dissolution Science and Applications (2018)

Formulation switch for a NCE

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





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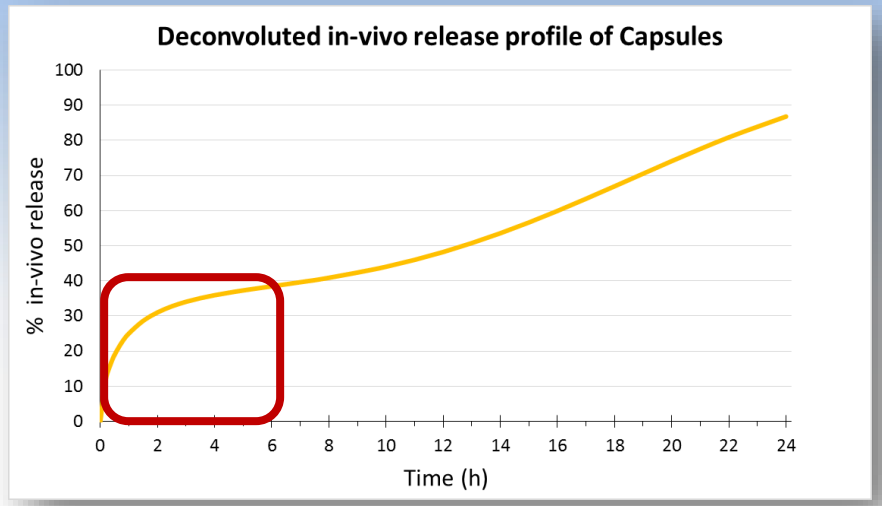
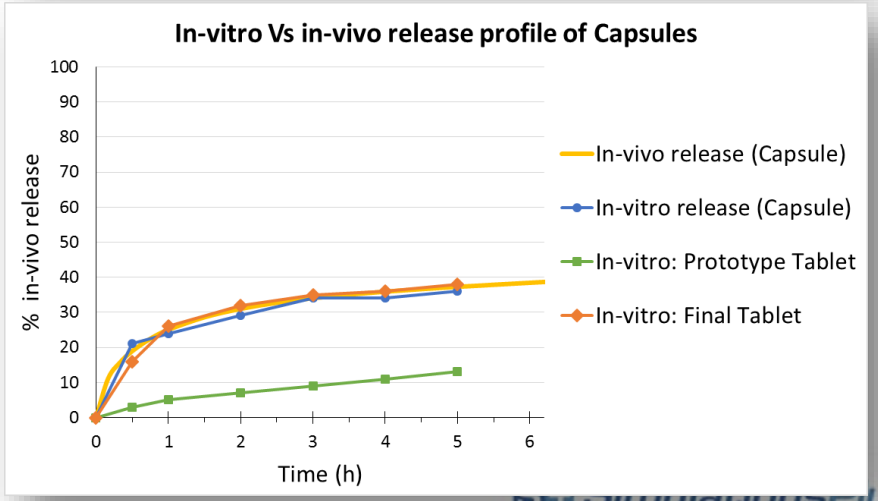
Formulation switch for a NCE

- Mechanistic deconvolution based on GastroPlus ACAT™ model coupled with systemic PBPK model:
  - *in vivo* precipitation followed by slow and sustained dissolution
  - C_{max} results from dissolution of only 20-40% of drug
- Biorelevant dissolution method:
  - Non-sink conditions
  - Optimization of tablet formulation for bridging study based on target deconvoluted profile from GastroPlus





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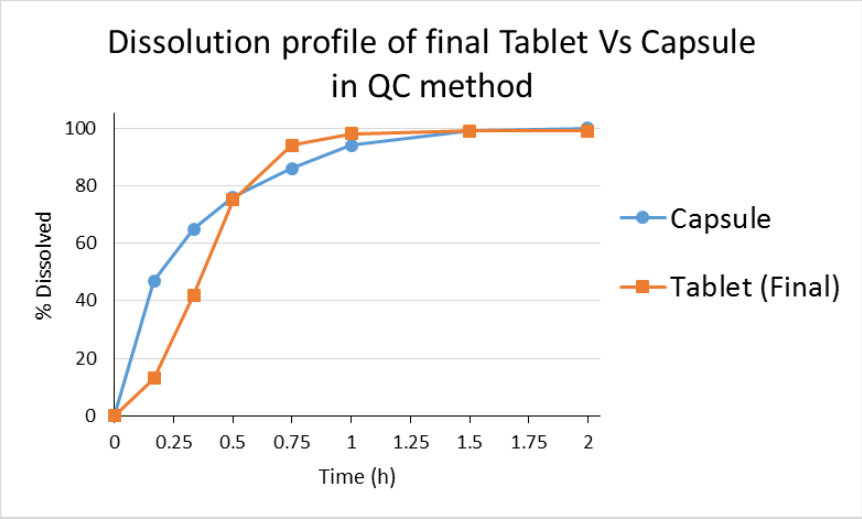
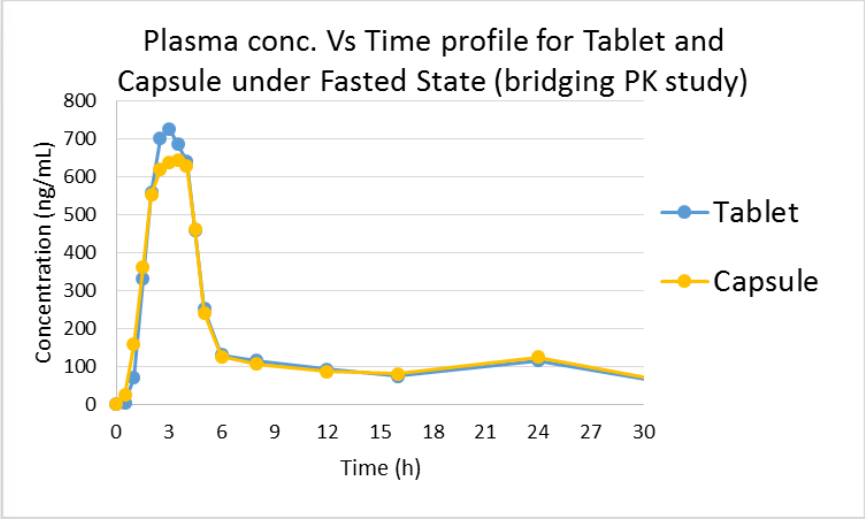
Formulation switch for a NCE

- Bridging PK study results:
  - Tablet was bioequivalent to capsule





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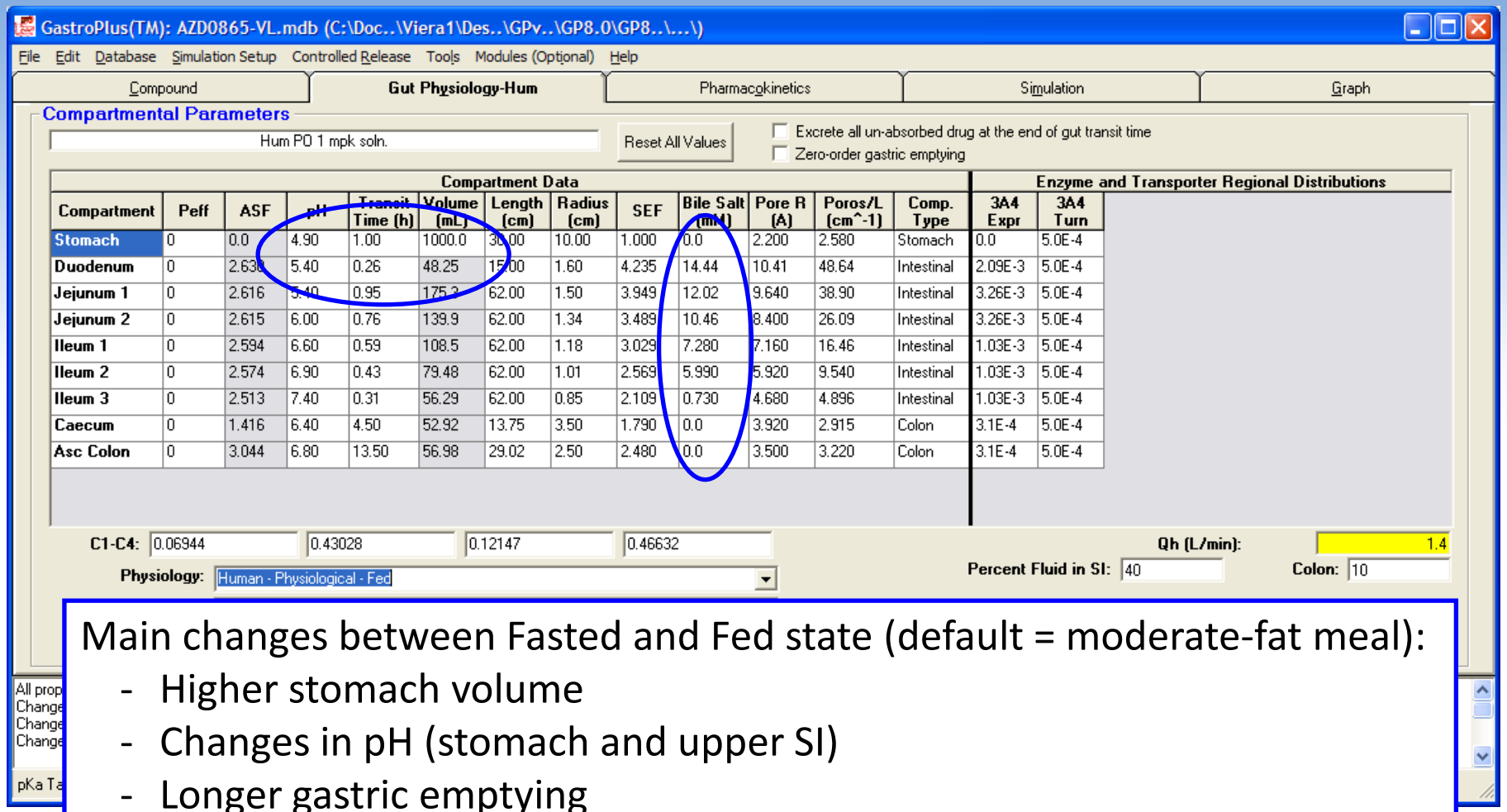
Understanding food effects to guide formulation development

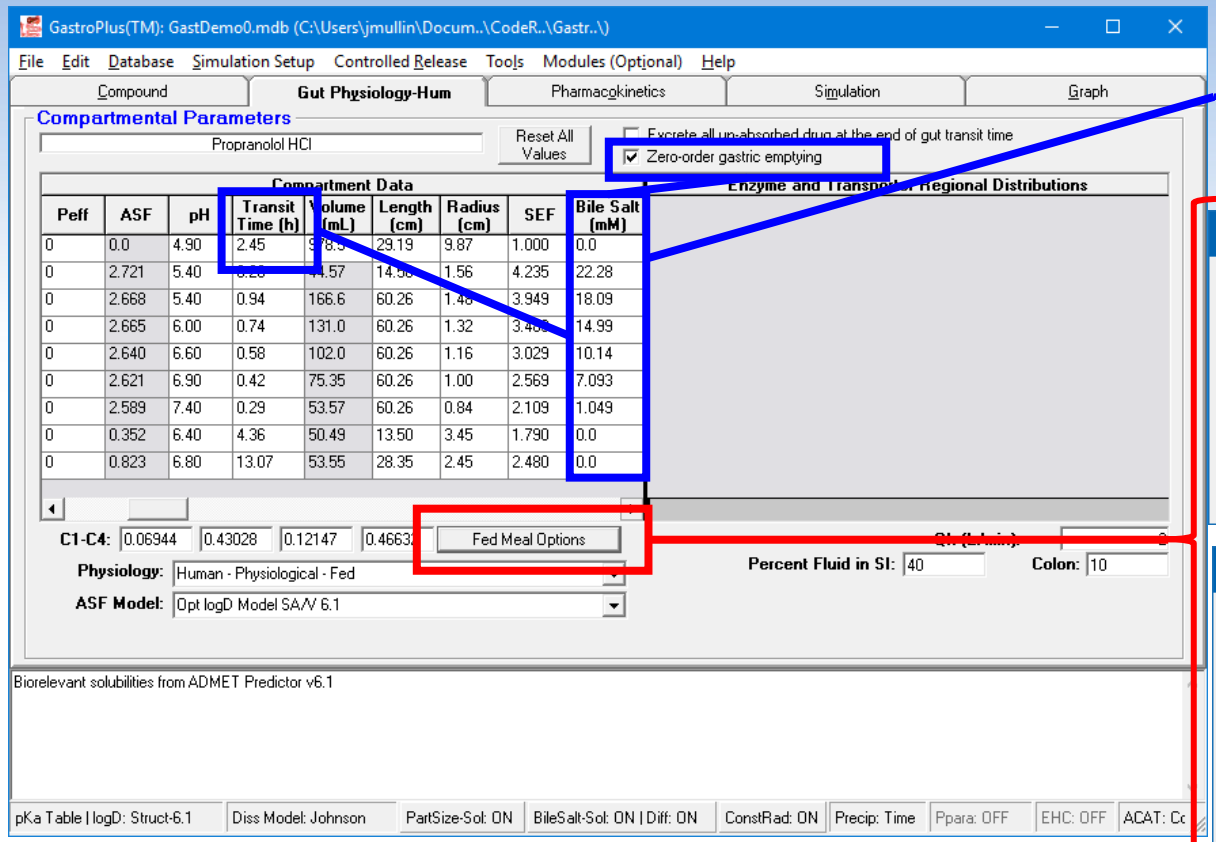
Fed State – GI physiology



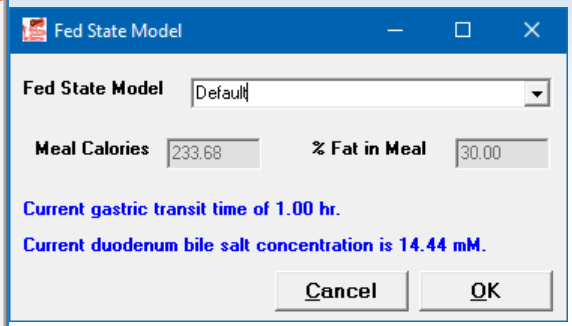
Main changes between Fasted and Fed state (default = moderate-fat meal):

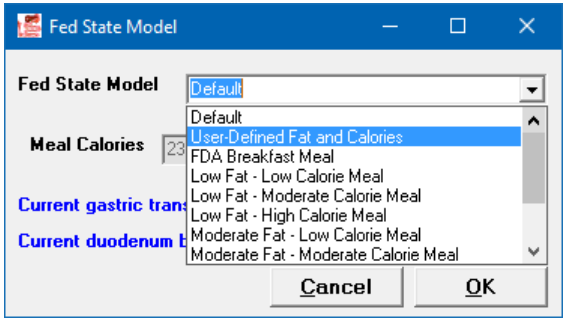
- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations
- Higher liver blood flow

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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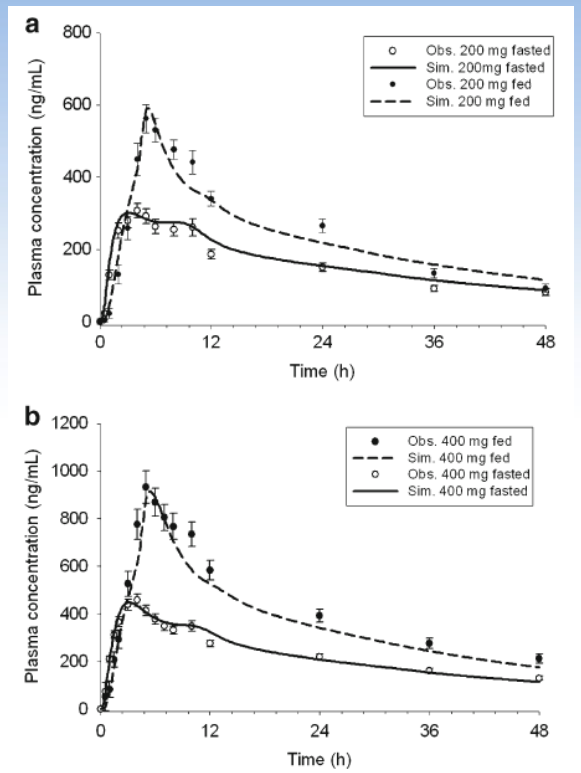
Analyzing multiple dimensions: Design of Experiments (DoE) approach

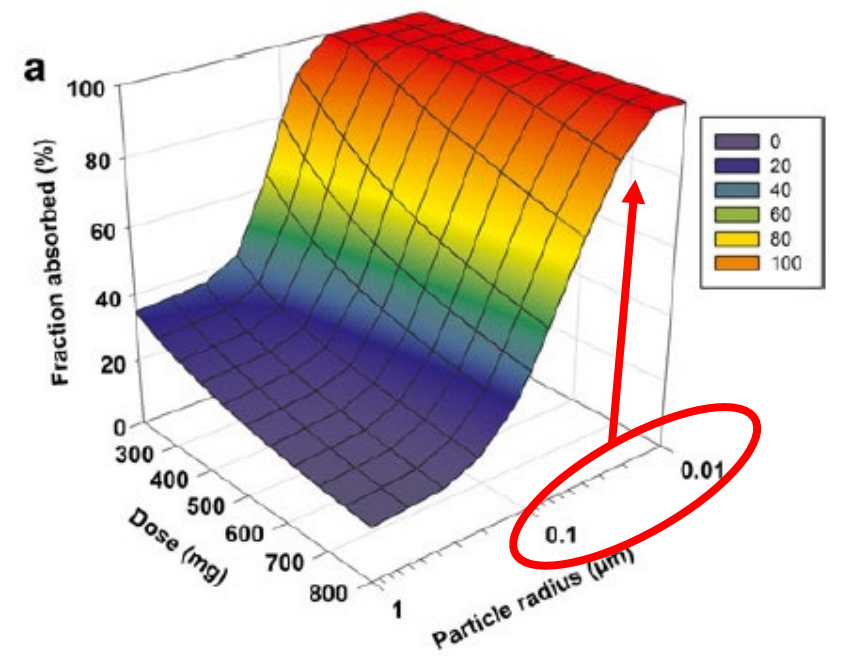
Parameters	Value(s)
Compound parameters	
M_w: g/mol	>475
cLogP:	>4
pK_a (base):	3.2, 6.2
Dosage:	IR capsule
Solubility (mg/mL):	1.8 (pH 1), 0.3 (pH 2), 0.001 (pH 6.8)
Biorelevant solubility (mg/mL) :	0.023 (fasted); 0.190 (fed)
Mean precipitation time (s) :	450 s (fasted); 2,000 s (fed)
Effective permeability (cm/s):	1.48×10^{-4}
Particle radius of API (μm):	19
Physiological parameters	
Stomach pH	1.2 (Fasted); 1.2–4.9 (Fed)
Duodenum/jejunum pH	6.0–6.4 (Fasted); 5.4–6.0 (Fed)
Ileum pH	6.6–7.4 (Fasted); 6.6–7.4 (Fed)
Cecum–colon pH	6.4–6.8
Stomach transit time (h)	2.0 (Fasted); 5.4 (Fed)
Small intestine transit time (h)	3.3
Cecum transit time (h)	4.2
Ascending colon transit time (h)	12.6
Pharmacokinetics	
First pass extraction (%):	9.0
Blood/plasma ratio:	0.68
Plasma unbound (%):	1.6
Clearance (L/h/kg)	0.070
V_c (L/kg)	0.4
k_{12} (1/h)	0.64
k_{21} (1/h)	0.17
V_t (L/kg)	1.5



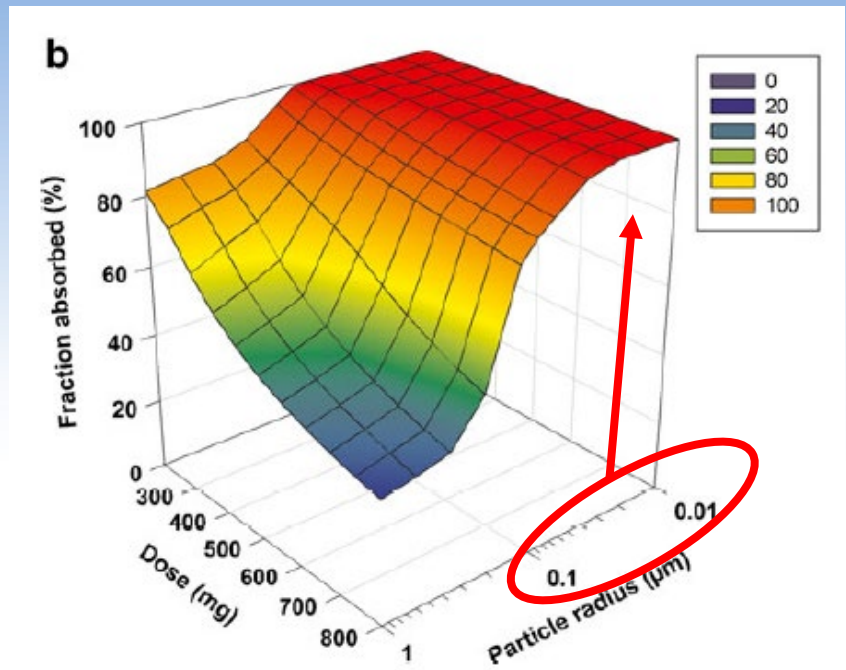
- Baseline models in GastroPlus were developed to predict the food effect for a weak base compound across different doses
- Is there an optimal combination of formulation parameters that allow us to reach our target endpoint (e.g., Fa%, Cmax, AUC)?

Zhang et al. AAPS PharmSciTech 2014 January 17

3D Parameter Sensitivity Analysis



Fasted

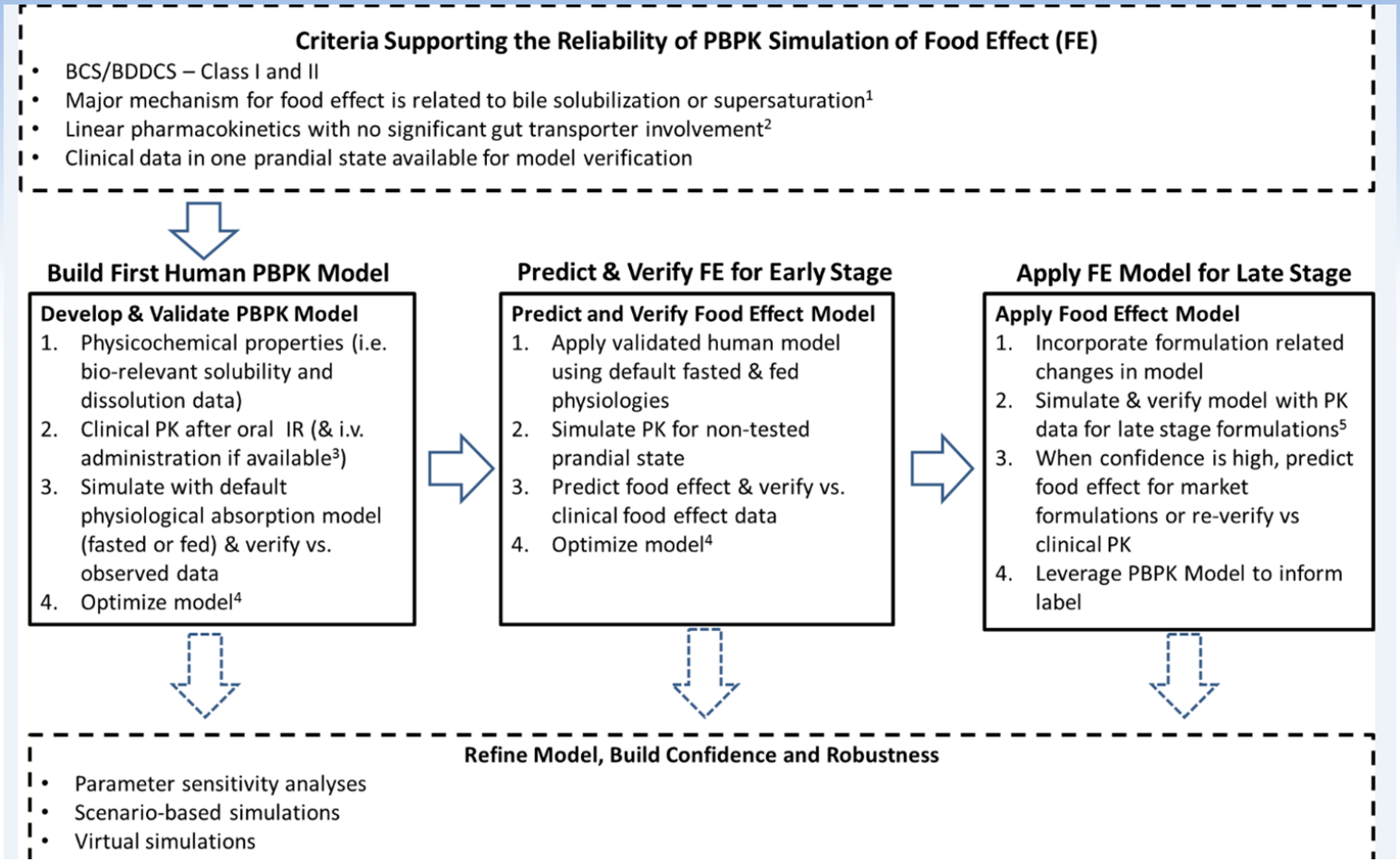


Fed

- Parameter sensitivity analysis was run across dose and particle size together
- API particle size reduction may be useful to mitigate the food effect

Zhang et al. AAPS PharmSciTech 2014 January 17

Food effect projections via PBPK modeling: Predictive case studies



Tistaert et al. J. Pharm. Sci. (2018) Jun 12

Virtual crossover trials to show BE and establish particle size specification 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?

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

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

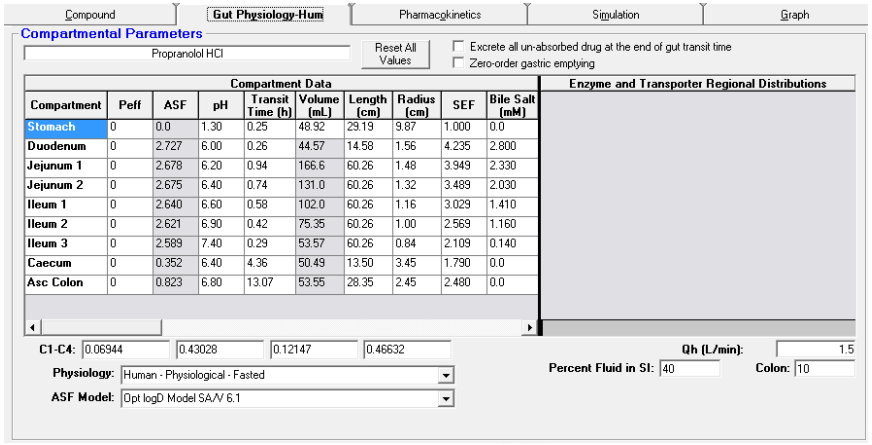
Parameter	Value
CL	0.115 L/h/kg
First pass extraction	17%
Vc	0.324 L/kg
K12	0.26 h^{-1}
K21	0.1 h^{-1}

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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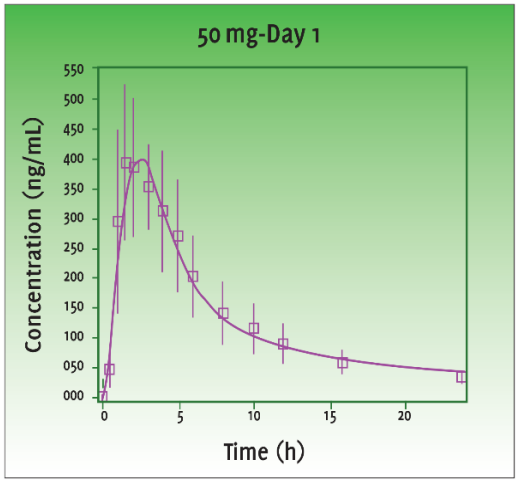
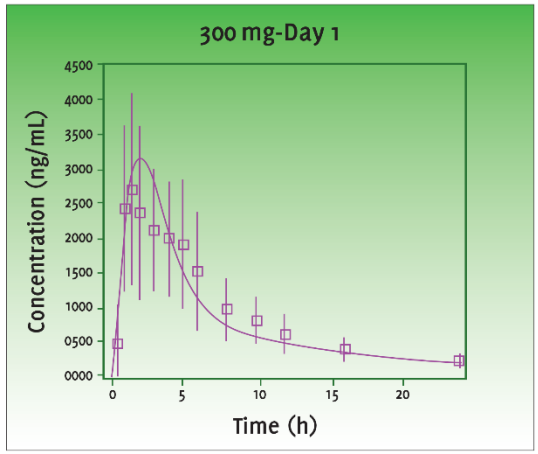
Part I: Simulation results for baseline models of non-engineered lots



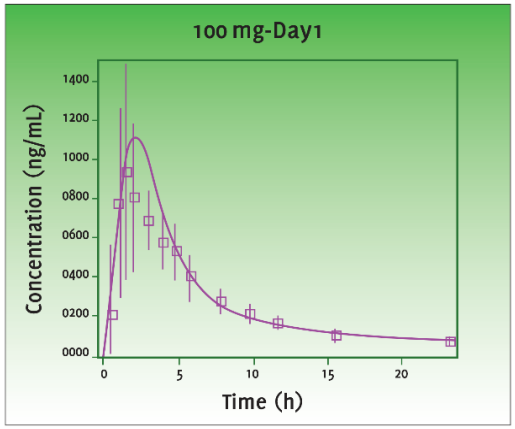
Total simulation time (h): 24

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

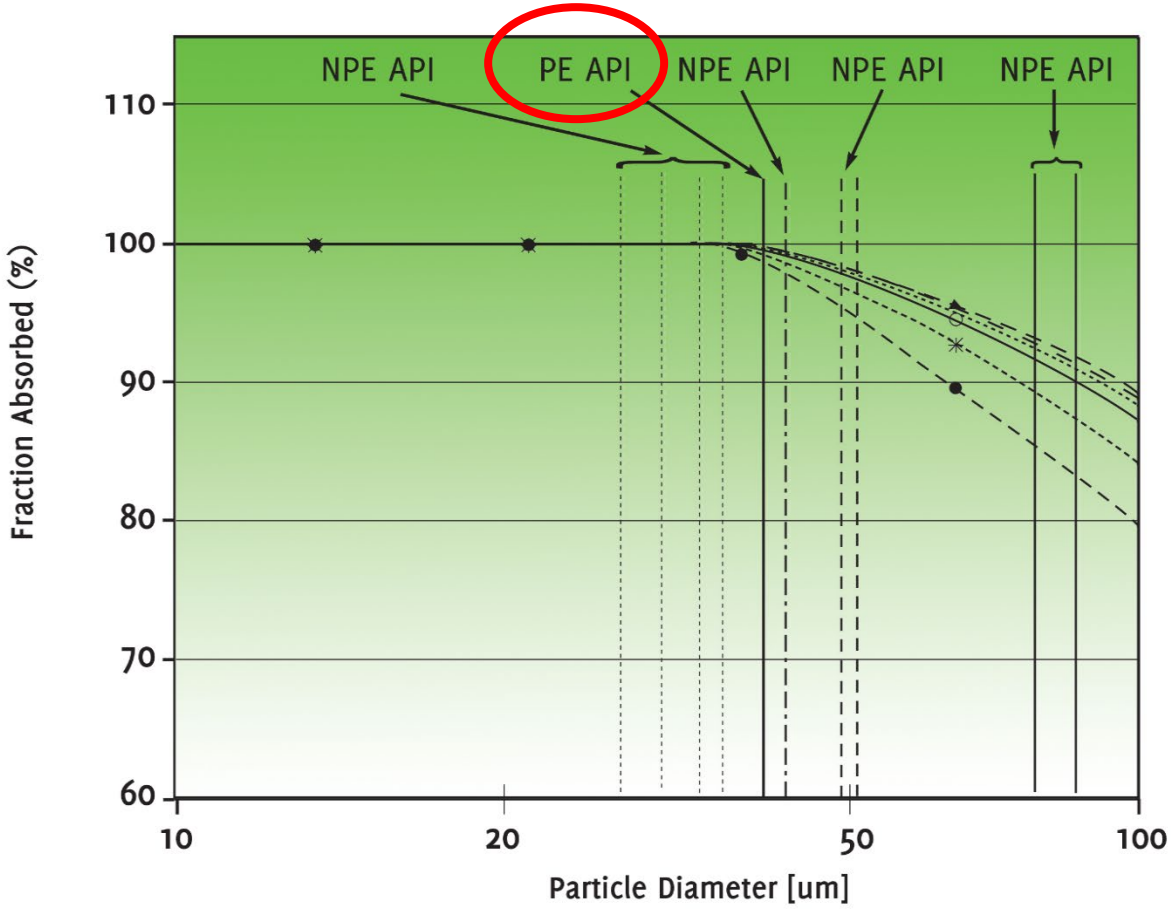


Total simulation time (h): 24

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.

Part II: Parameter Sensitivity Analysis (PSA) around mean particle radius: Dose range: 10 – 1000 mg



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.

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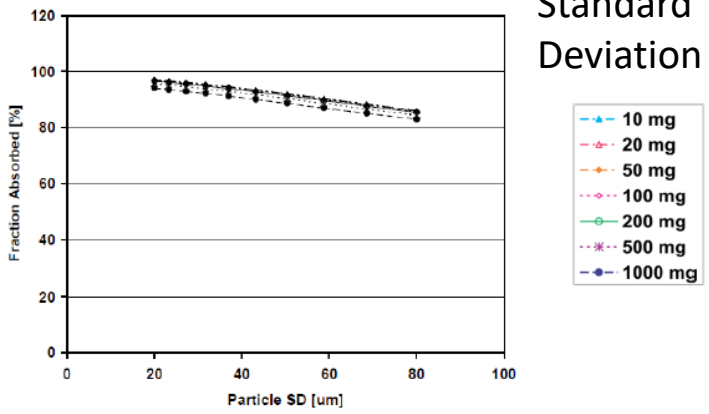
Part II: Parameter Sensitivity Analysis (PSA) around standard deviation & shape factor: Dose range: 10 – 1000 mg

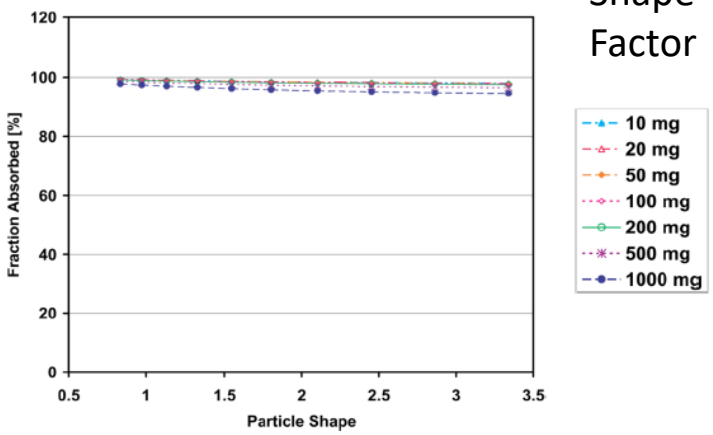
PSA was also run to evaluate changes in particle size standard deviation (assuming mean remained constant) and particle shape factor

Results indicated that there would be insignificant/moderate changes in Fa% across the range of values evaluated

Standard Deviation



Shape Factor



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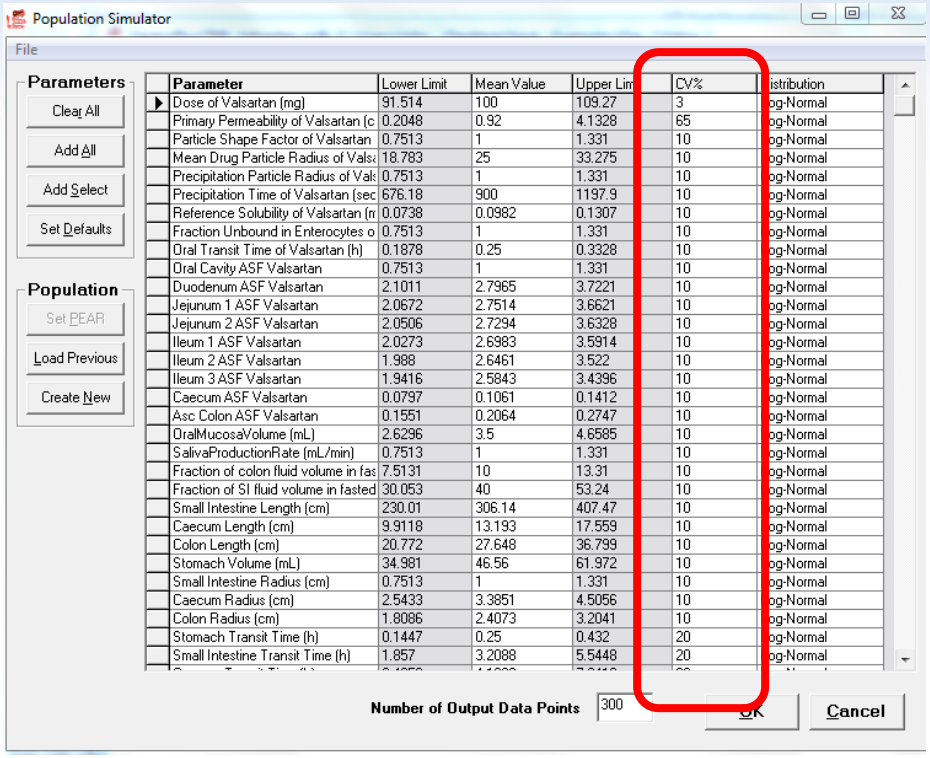
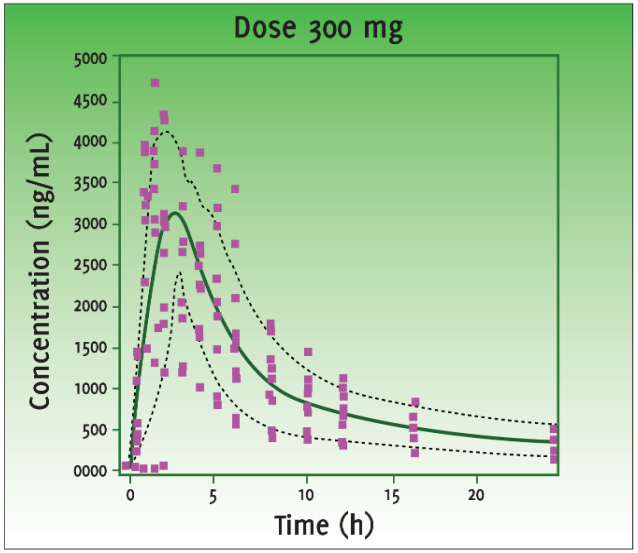
Part III: Virtual bioequivalence trials: Population Simulator™

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

Capture observed variability from existing clinical PK studies





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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

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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**
- **Sponsor got to market ~12 months before it would have running the full trials**

Conclusions

How PBBM/PBPK 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**

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Products & Services

Software Portfolio

- PBBM/PBPK modeling & simulation platform for R&D
- Machine learning technology for ADMET endpoints
- QSP/QST software for certain biological or disease states
- Population PK/PD functionality for pharmacometricians

Consulting Services

- Provide multi-disciplinary modeling and simulation support from discovery through post approval

Corporate Information

- Company founded in 1996 and now has >130 employees worldwide.
- Primary offices located in Los Angeles, CA; Buffalo, NY; Raleigh, NC; and Paris, France

Operating Divisions

- Simulations Plus, Inc.
- Cognigen Corporation
- DILIsym Services
- Lixoft

Consistent Financial Results/Investments

- Publicly traded (NASDAQ: SLP)
- > 10 years of consistent revenue growth
- > 10 years of profitability
- Invest ~10% of revenue into software R&D

Customers and Market

- >250 pharmaceutical, biotechnology, chemicals, and consumer goods companies in the U.S., Europe, Asia, and South America
- Most major regulatory agencies (U.S. FDA, EMA, PMDA, NMPA, Health Canada) have reviewers trained on our technology
- >1000 peer-reviewed journal articles and conference presentations citing software

>1100 members on the LinkedIn group page – membership is free!

GastroPlus® User Group on LinkedIn

Mission & Goals:

Discuss best practices, Q&A and FAQs
Share knowledge of software functionality and applications
Publish journal articles to show validation for different applications
Present and advance M&S science via social media, webinars and face-to-face meetings
Feedback on improvements and software functionality requests to Simulations Plus
Understand and influence regulatory expectations for M&S submissions