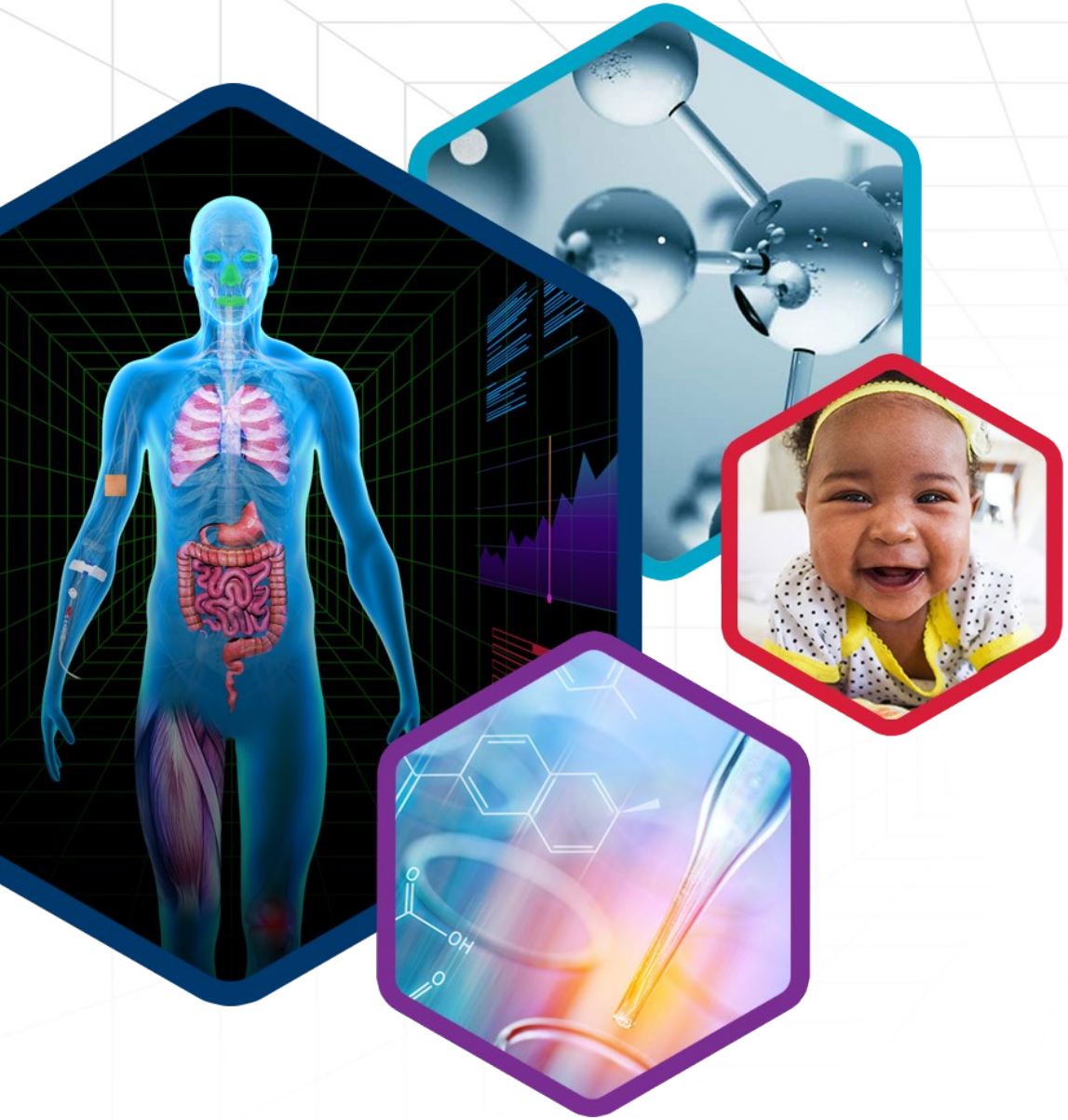

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Data required to build a fit-for-purpose PBPK model: How much is necessary?

Anant Ketkar, Ph.D.
Scientific Lead – India, Simulations Plus, Inc.

Disso India 2022: June 23-25, 2022

Agenda

- A Brief Introduction to PBPK M&S and PBBM
- A Magic Wand Without Any Data Vs Requires Too Much Data!!!
- Modelling Tools by Simulations Plus, Inc. 
- Where Does PBPK / PBBM Stand in Generic DP Development Path
- Applications of PBPK / PBBM in Generic DP Development
- Data In-Hand and Possibilities: Case Study
- Prioritizing and Designing Experiments
- Regulatory Acceptance and Growing Visibility of PBPK M&S
- Concluding Remarks

PBPK M&S and PBBM

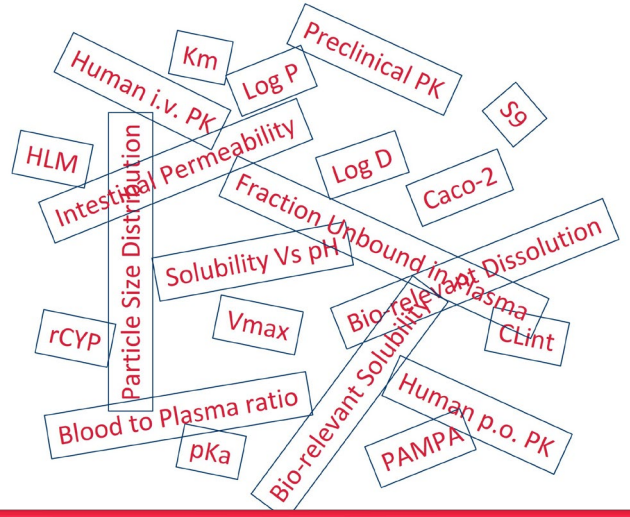
PBPK Modeling: Physiologically Based PharmacoKinetic Modelling

- A mathematical modelling technique for predicting the ADME of synthetic or natural chemical substances in humans and other animal species

PBBM: Physiologically Based Biopharmaceutics Modelling

- Establishing the link between bio-predictive *in vitro* dissolution testing and mechanistic oral absorption modeling
  - Mechanistic implementation of formulation/manufacturing aspects that are relevant to dissolution/release from the drug product
  - Verifying whether the dissolution method of the pharmaceutical product is bio-predictive or clinically relevant

A Magic Wand Without Any Data Vs Requires Too Much (Experimental) Data!!!



Perception

- '*in silico*' = 'magic wand'; 'no data required'
- 'requires too much data'
- 'better to conduct a clinical PK study'

Expectations

- Minimal experimental input data
- Model development, validation in a week or max. in a couple of weeks!
- Zero/Minimal prediction error!

A Magic Wand Without Any Data Vs Requires Too Much Data!!!

Early NCE/Generic Research I Exploratory

- Screening of compounds
- Pre-clinical
- Risk assessment / Flags
- Defining formulation strategy
- CMAs

PURPOSE of developing a PBPK model is the KEY

Regulatory I Biowaivers

- Dissolution safe space
- Revision of SPECs
- Bio-waivers
  - Lower/Higher strengths
  - Substituting Clinical Equivalence study
  - DDI

Modelling Tools by Simulations Plus, Inc.

GastroPlus®

A mechanistically-based simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal, subcutaneous, intramuscular, and intraarticular absorption, biopharmaceutics, pharmacokinetics, DDI, and pharmacodynamics in humans and animals

ADMET Predictor®

A machine learning software tool that quickly and accurately predicts over 175 properties, including solubility, logP, pKa, sites of CYP metabolism, and Ames mutagenicity

DDDPlus™

Mechanistic *in vitro* dissolution software for formulation and analytical scientists

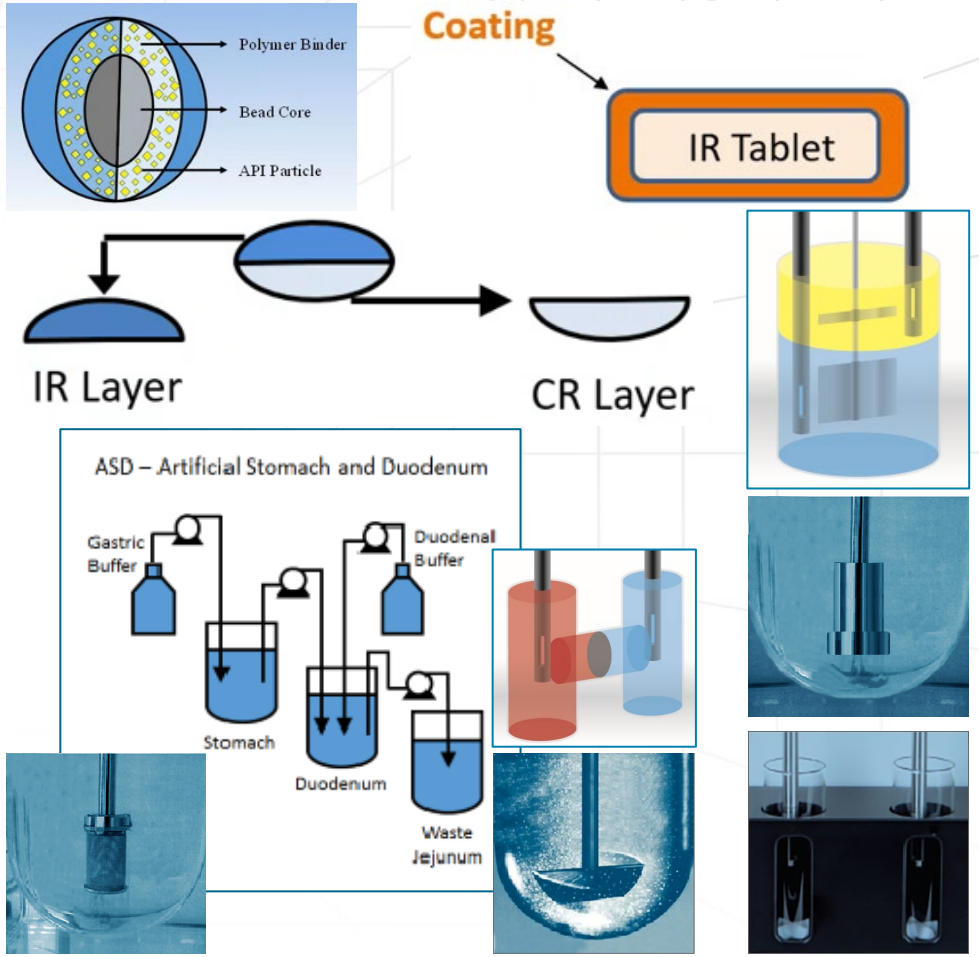
MembranePlus™

Mechanistic *in vitro* permeability & hepatocyte modeling software

Modelling Tools by Simulations Plus, Inc.

DDDPlus™

- Dissolution rate of API and excipients
- Variety of Dosage Forms
  - IR: Powder, Tablet, Capsule, Bead coating (drug-layered pellets), Solution (with precipitation)
  - DR: Coated tablet
  - CR: Polymer matrix (swellable and non-swellable), Bilayer tablets (IR + CR layers), Coated beads
  - Long-acting injectables: PLGA microspheres
- Options for dissolution apparatus and conditions
  - USP 1, USP 2, USP 4 flow-through (open and closed loop)
  - Pion µDiss Profiler™, Artificial Stomach Duodenum (ASD), Membrane dissolution, Biphasic dissolution, Rotating Disc
  - Standard aqueous pH buffer systems, with/without surfactants and intestinal bio-relevant media
  - Media change-over methods



Where Does PBPK Stand in Generic DP Development Path?

Project Initiation
- **Formulation strategy**
- **Clinical /BE strategy**
- **Risk assessment**

Prototype development
- Formulation, process feasibility/ scalability
- **Bio-relevant method development**

Pilot BE study
- **Reformulation?**

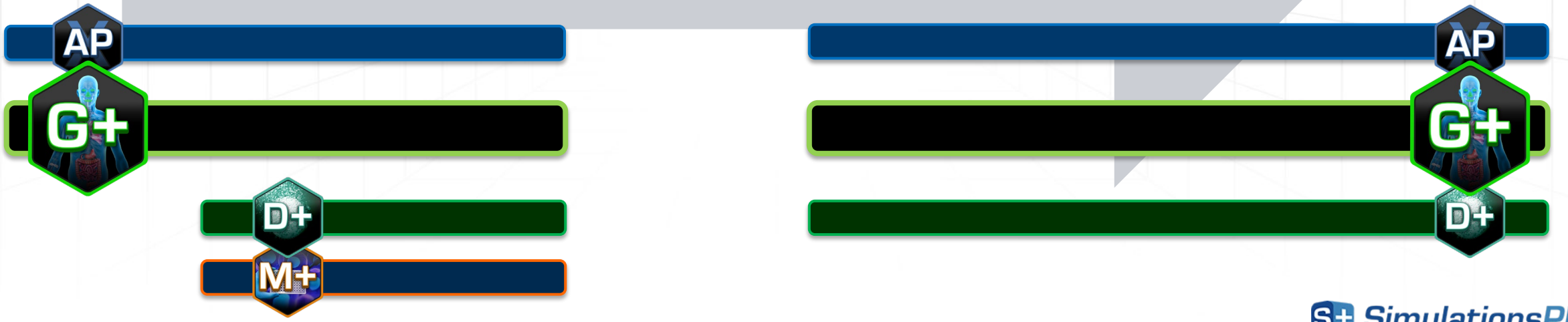
Technology transfer
- Scale-up
- Exhibit batches
- Stability studies

Pivotal BE study
- **Failure to meet BE criteria?**

Regulatory review
- Deficiencies / Requests by agency for **additional clinical/PK studies**
- **Bio-waiver for lower/higher strengths**

Approval and launch
- Process validation
- **Challenges in meeting SPECs**

Post-approval changes
- Variation batches
- **Bio-waiver / Bridging PK**
- **Revision of SPECs**

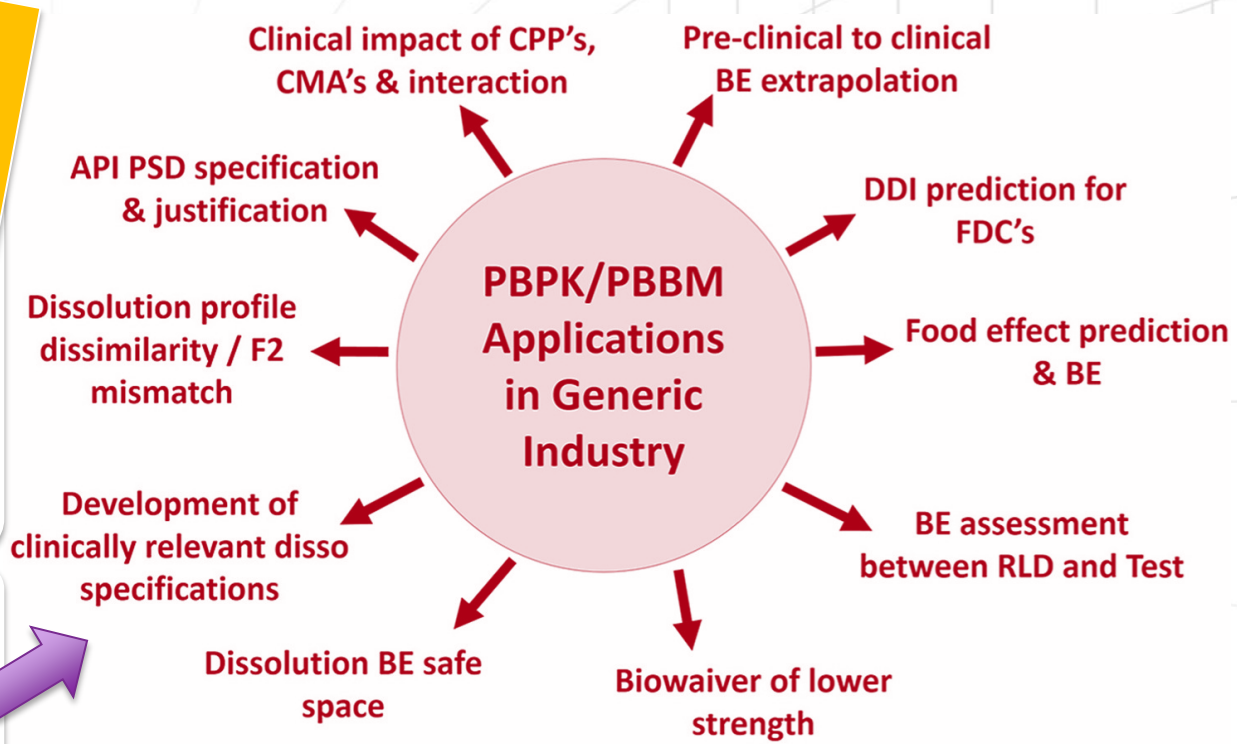


Applications of PBPK / PBBM in Generic DP Development

- Defining formulation strategy
  - Key API and DP attributes
- Prioritization of experiments
- IVIVE for pilot BE
- IVIVC for exploratory and/or regulatory purpose
- Design space
- Risk assessment

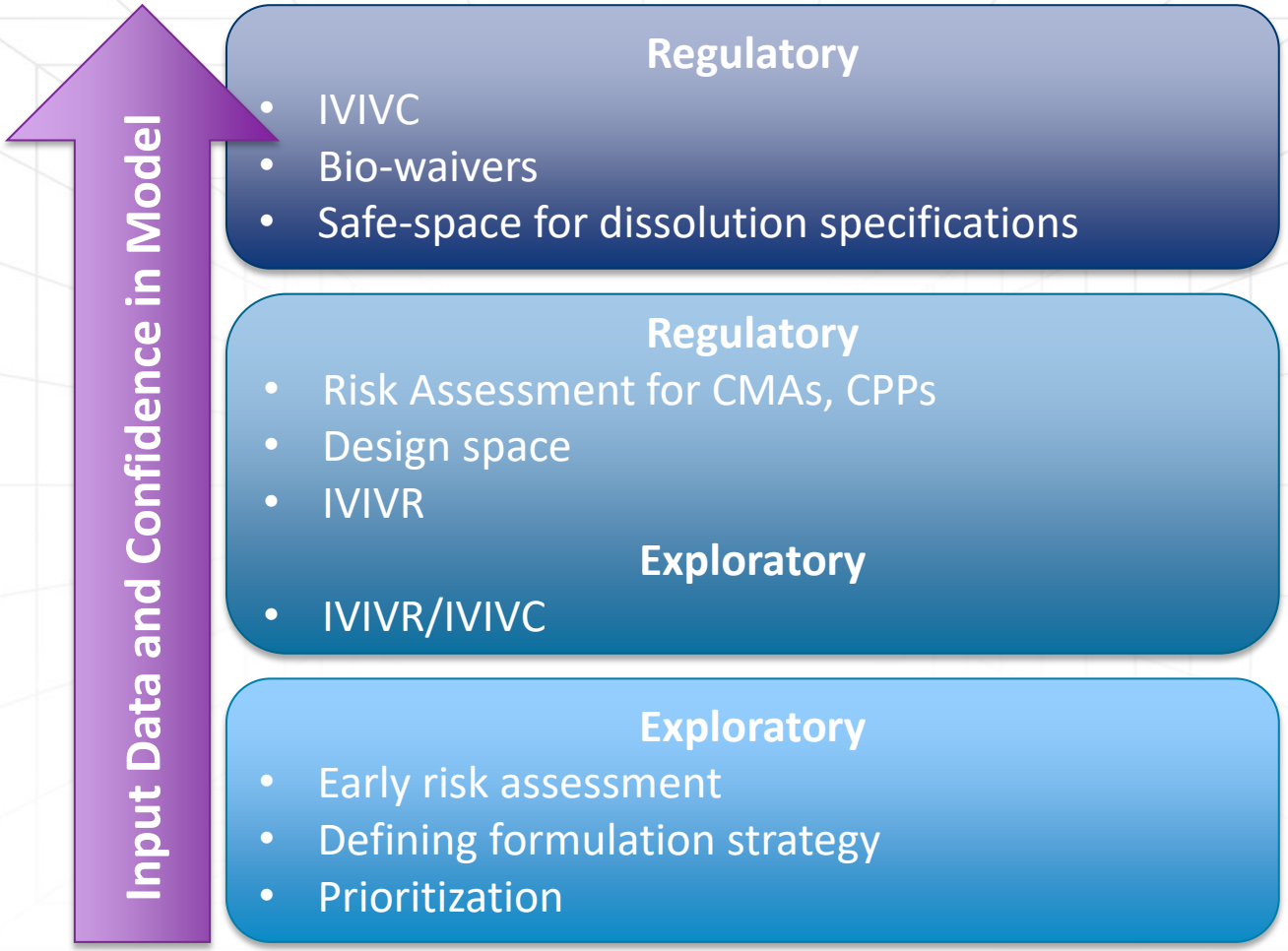
- Understanding the influence of compound, formulation and process attributes
- Gaining insights
- Informed decision making

- Regulatory review
- Justifying changes
- Bio-waivers
- New dosage form/regimen [505(b)(2)]
- DDI for FDCs



Yuvaneshwari, Kollipara, S., Ahmed, T., & Chachad, S. (2022). Applications of PBPK/PBBM modeling in generic product development: An industry perspective. Journal of Drug Delivery Science and Technology, 69(103152), 103152. doi:10.1016/j.jddst.2022.103152

Data In-Hand and Possibilities



Case Study: Lurasidone

Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

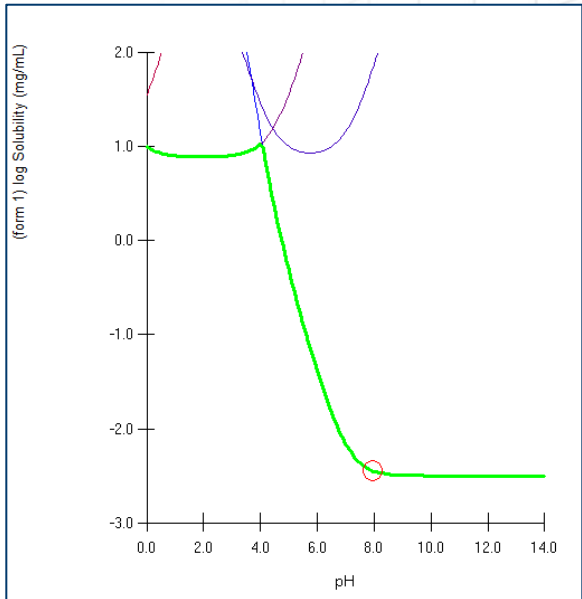
Compound Name	Lurasidone
Drug Substance	Lurasidone Hydrochloride
Reference Product (RLD)	Latuda
Strengths	20, 40, 60, 80, 120 mg
Reference Standard	Latuda 40 mg
Dosage Form	Film coated IR Tablet
BE recommendations	Single-dose, two-way crossover *in vivo* studies under Fasted and Fed states using 40 mg (safety concerns) in healthy males and nonpregnant females
Administration	Latuda should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of Latuda.

Case Study: Lurasidone

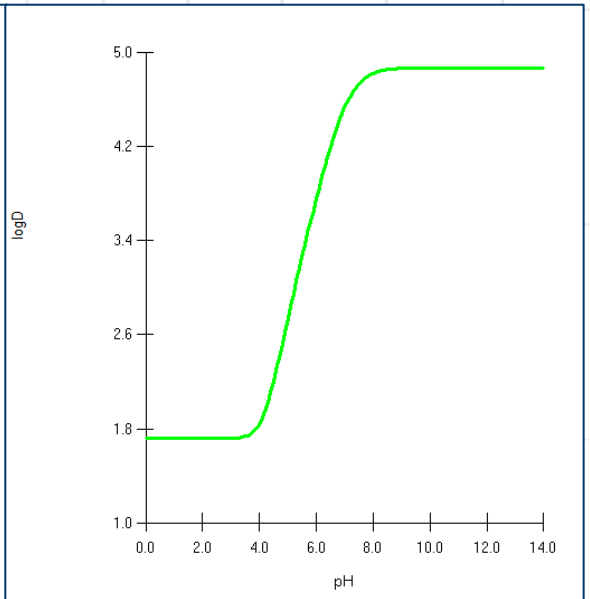
Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

- *In silico* structure-based predictions using ADMET Predictor™: Compound Properties

Parameter	Value / Likelihood
Log P	4.87
pKa	4.44 (base), 7.07 (base)
Solubility (mg/mL)	0.0036 @pH 7.94
Peff (cm/s)	4.04 x 10^-4
Biorelevant solubility (mg/mL)	SGF = 4.85, FaSSIF = 0.00448, FeSSIF V2 = 0.0157
Solubilization ratio (bile salt effect)	1.59 x 10^5



Solubility Vs pH Profile



Log D Vs pH Profile

Case Study: Lurasidone

Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

- *In silico* structure-based predictions: Notes (flags, classifications etc.)

Parameter	Value / Likelihood
Likelihood of BBB Penetration@	High (99%)
ECCS Classification^	Class_2 (Metabolism)
S+ Mechanistic Clearance Classification	Metabolism
Transporter Inhibitor Classification:	
OATP1B1-Inhibitor	No (52%)
OATP1B3-Inhibitor	Yes (82%)
OCT1-Inhibitor	Yes (94%)
OCT2-Inhibitor	Yes (92%)
OAT1-Inhibitor	No (94%)
OAT3-Inhibitor	No (94%)
P-gp-Inhibitor	Yes (88%)
BSEP-Inhibitor	Yes (83%)
BCRP-Inhibitor	No (76%)
Transporter IC50 Values:	
BSEP-IC50	17.18uM

Parameter	Value / Likelihood
Transporter Substrate Classification:	
OATP1B1-Substrate	Yes (42%)
OATP1B3-Substrate	Yes (68%)
OCT1-Substrate	No (89%)
OCT2-Substrate	Yes (52%)
OAT1-Substrate	No (92%)
OAT3-Substrate	No
P-gp-Substrate	Yes (82%)
BCRP-Substrate	No (52%)
Transporter Km Values:	
OATP1B1-Km	2.44uM
OATP1B3-Km	0.36uM
OCT1-Km	NonSubstrate
OCT2-Km	44.36uM
OAT1-Km	NonSubstrate
OAT3-Km	NonSubstrate

@ Passive process

^ Varma, M. V., Steyn, S. J., Allerton, C., & El-Kattan, A. F. (2015). Predicting clearance mechanism in drug discovery: Extended Clearance Classification System (ECCS). Pharmaceutical Research, 32(12), 3785–3802.

Case Study: Lurasidone

Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

- *In silico* structure-based predictions: Metabolism and Compartmental Parameters

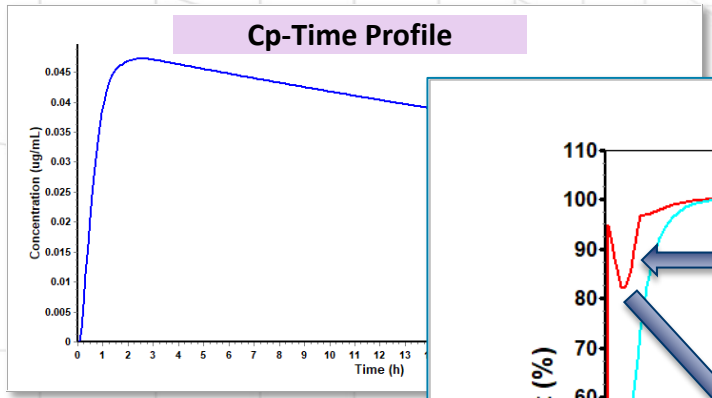
Enzyme	V_{max} (mg/s/mg-enzyme)	Km (mg/L)
CYP2D6	0.00181	9
CYP3A4	0.00574	5.09

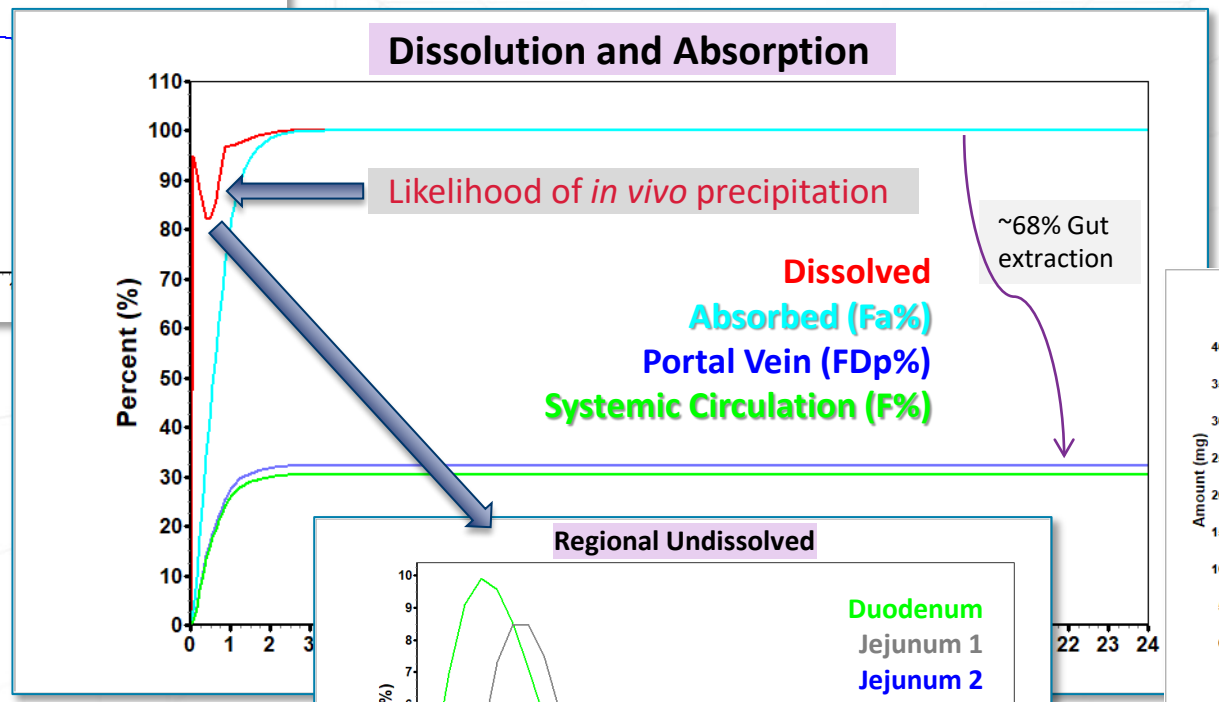
Parameter	Predictive Model	Value
Vc	-	3.46 L/kg
CL & $t_{1/2}$	Total liver microsome	0.84 L/h; 200 h
	Hepatocytes	1.45 L/h (+ Liver FPE 2.06%); 116 h
	3A4 HLM + other rCYPs	25.47 L/h (+ Liver FPE 36.14%); 7 h

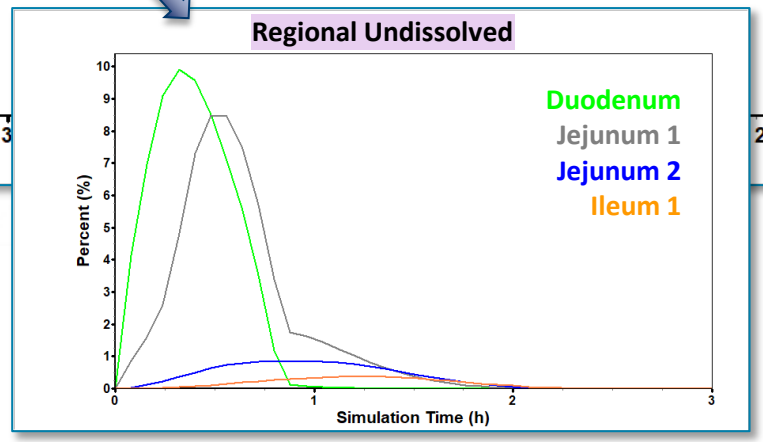
Case Study: Lurasidone

Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

- *In silico* structure-based predictions: Simulation

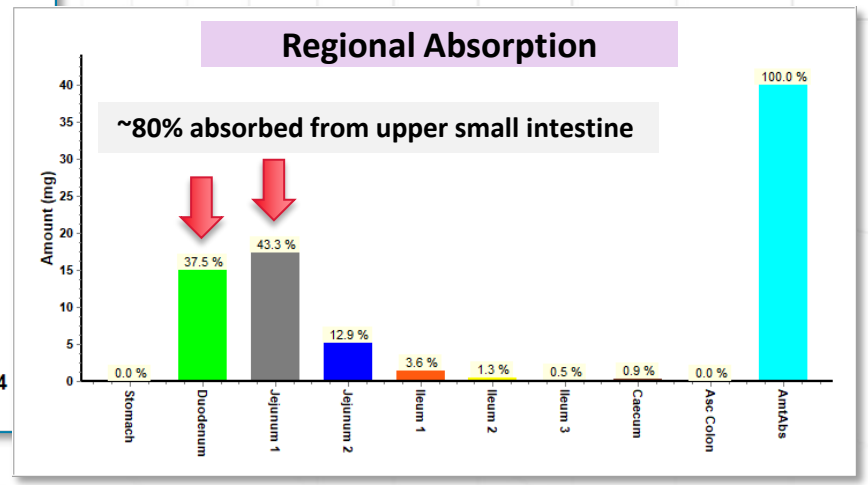







```
Record:   Lurasidone AP10.3_rCYP
Total simulation time (h):   24

Result                  Observ    Simul
Fa (%):                  0        100.00
FDp (%):                 0         32.31
F (%):                  14         30.45
Cmax (ug/mL):           0.043      0.047
Tmax (h):               2          2.56
AUC 0-inf (ug-h/mL):    1.77E-4    2.841
AUC 0-t (ug-h/mL):      1.77E-4    0.941
CMax Liver (ug/mL):                0.232
```



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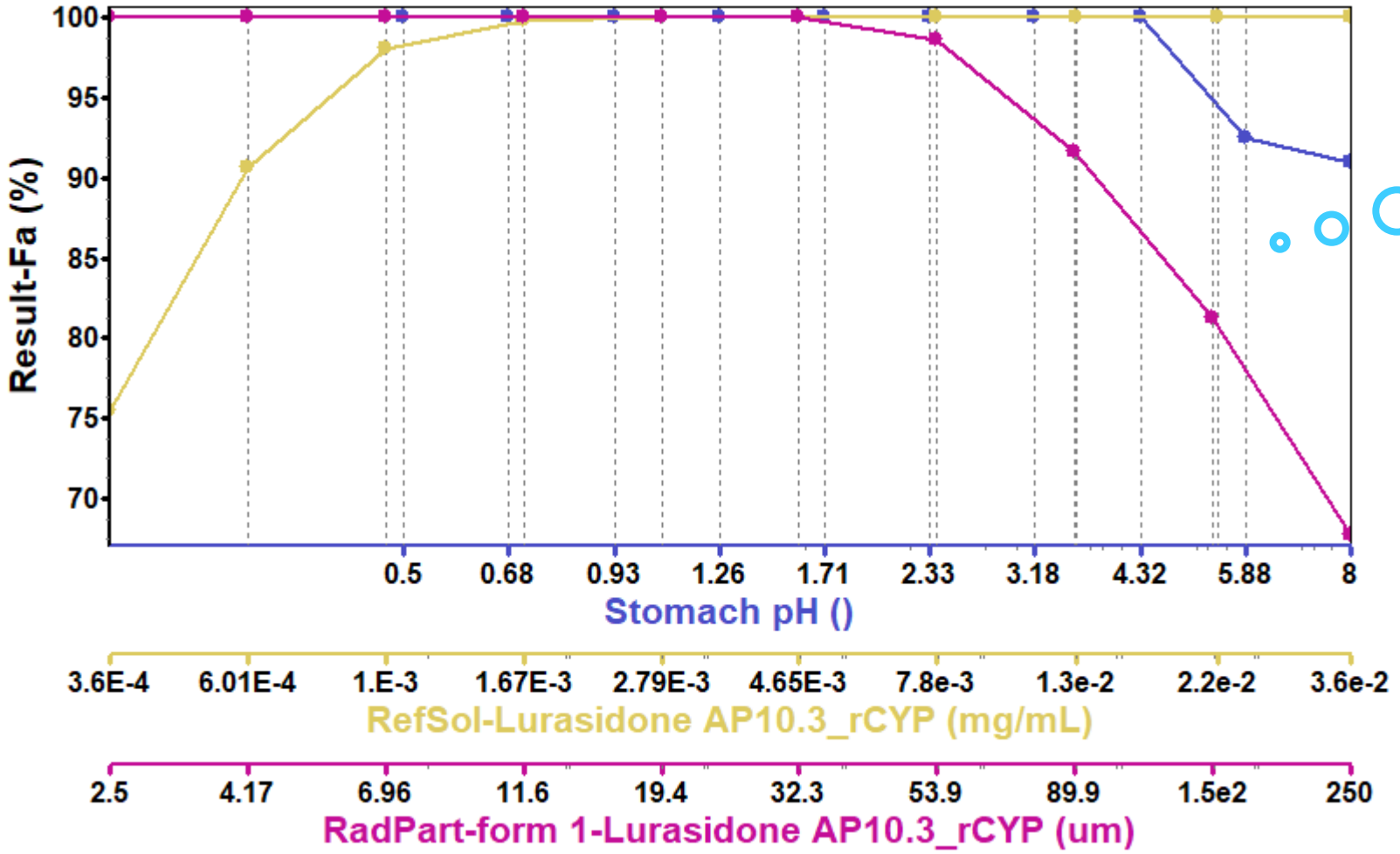
Case Study: Lurasidone

Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

- *In silico* structure-based predictions: PSA



Stomach pH
API Solubility
API Particle Size

Case Study: Lurasidone

Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

- *In silico* structure-based predictions + Literature: Fit for purpose model

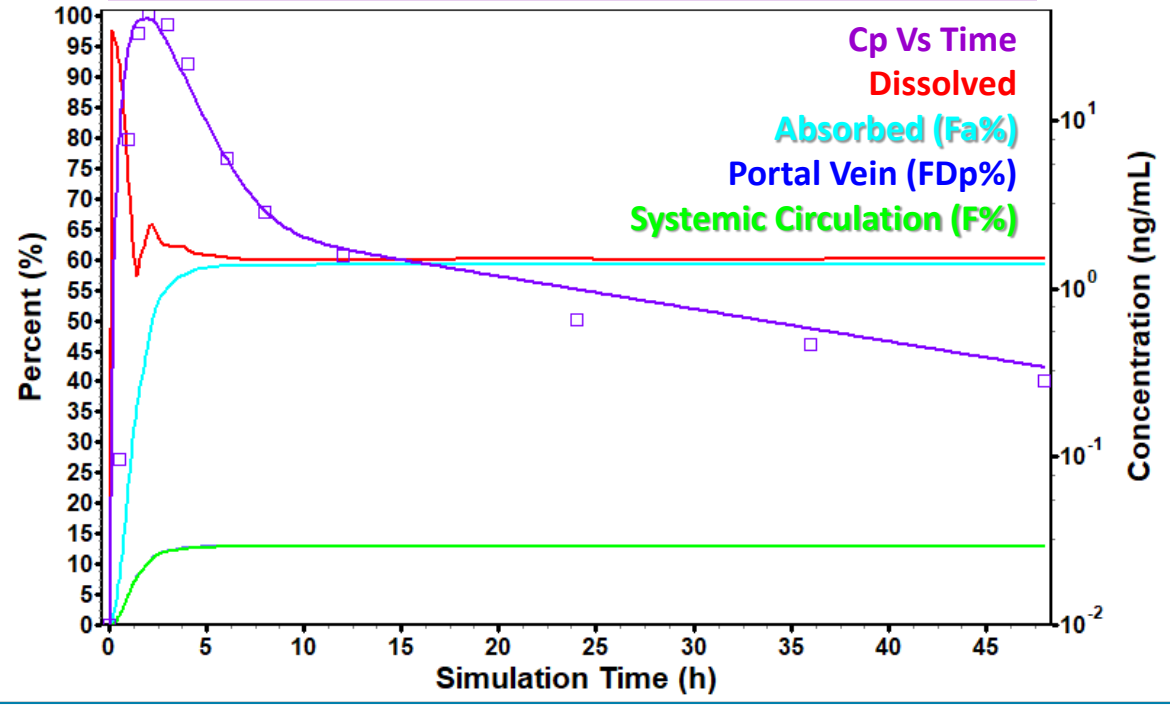
Key Input Parameters (Literature / Fitted)

- Log P, Fu/p, Rb/p, Intrinsic solubility
- Three-compartment PK parameters (corrected for F)
- CYP3A4 V_{max} and Km (common for gut and liver)
- P-gp apical efflux V_{max} and Km (gut)

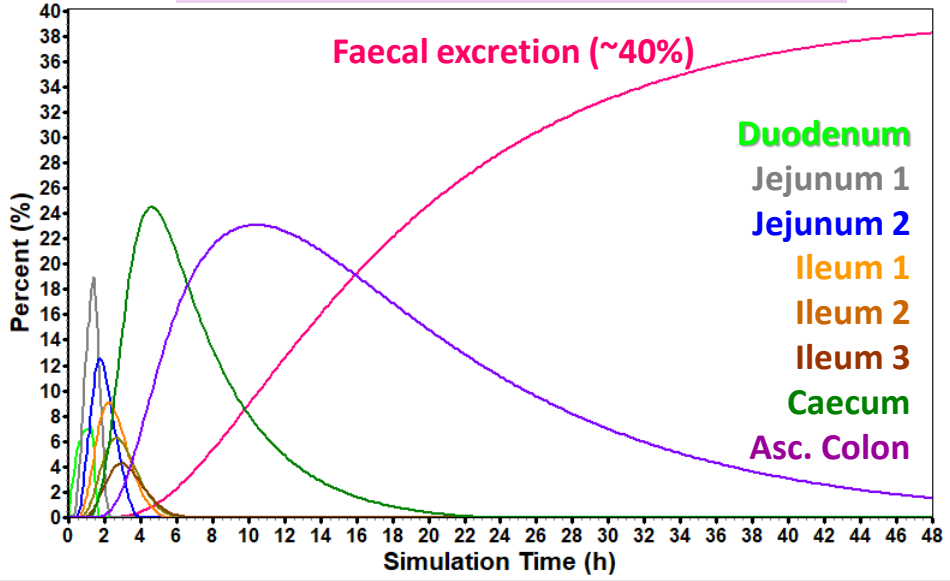
```
Record:    Hu2017_PO 40 mg_CYP+P-gp
Total simulation time (h):    48

Result                  Observ    Simul
Fa (%):                  0        59.24
FDp (%):                 0        12.99
F (%):                   14       12.89
Cmax (ng/mL):            43.13    39.91
Tmax (h):                2        1.86
AUC 0-inf (ng-h/mL):     177.6    180.4
AUC 0-t (ng-h/mL):       170.9    172.6
CMax Liver (ng/mL):               65.41
```

Cp-Time Profile and Dissolution and Absorption



Regional Undissolved and Faecal excretion

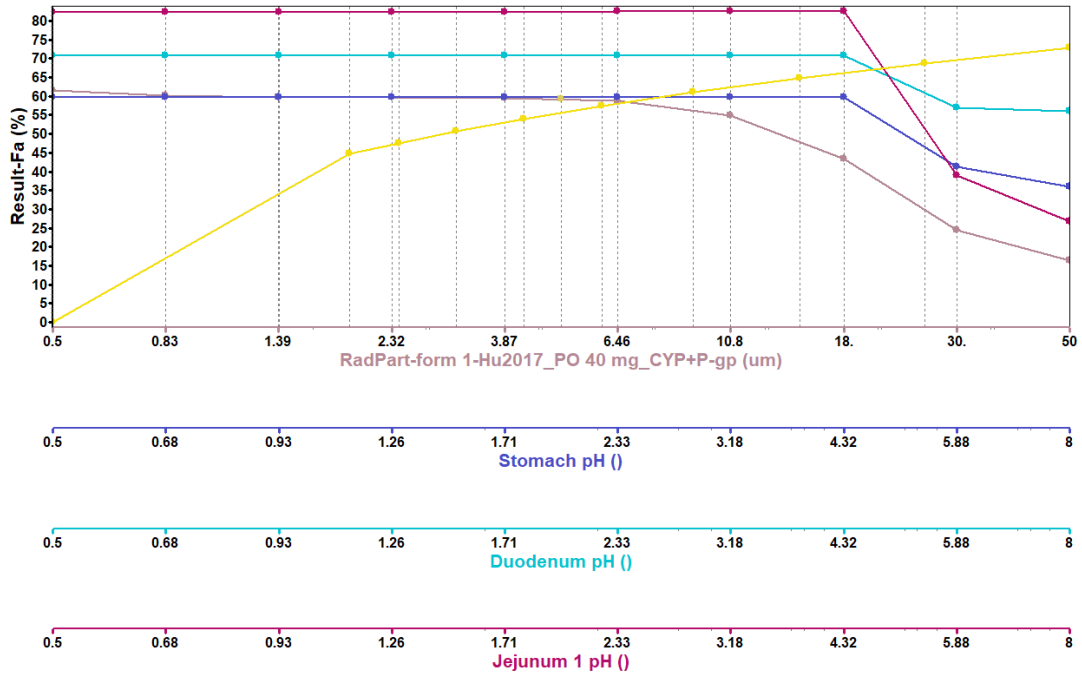


Case Study: Lurasidone

Exploratory | Early risk assessment | Defining formulation strategy | Prioritization

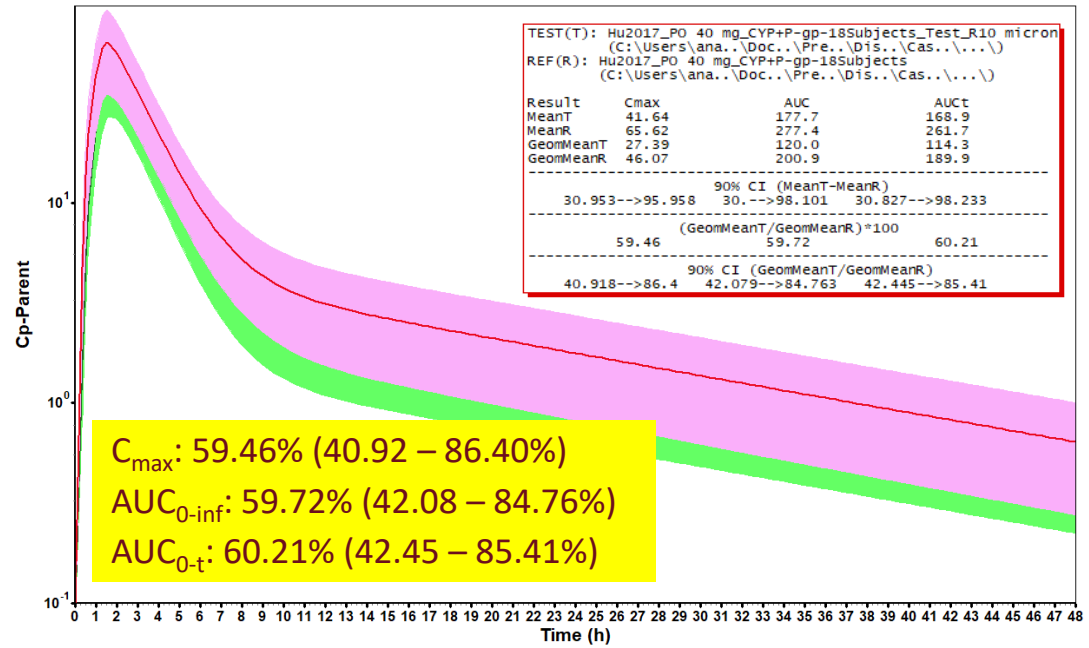
- *In silico* structure-based predictions + Literature: Fit for purpose model

Parameter Sensitivity Analysis



- **Regional pH in the Stomach, Duodenum, Jejunum 1**
- **API Particle Size**
- **SITT**

Effect of API Particle Size (mean diameter)
Test = 20µ Vs Ref = 10µ



C_{max}: 59.46% (40.92 – 86.40%)
$AUC_{0\text{-}inf}$: 59.72% (42.08 – 84.76%)
$AUC_{0\text{-}t}$: 60.21% (42.45 – 85.41%)

Prioritizing and Designing Experiments

Prioritizing

- Solubility?
- Permeability?
- *In vitro* metabolism?
- Bio-relevant solubility?
- Log D?
- Precipitation kinetics?
- *In vitro* metabolism kinetics?

Designing

- Fed state mimicking dissolution
- Gastro Intestinal Simulator
- pH - precipitation

Regulatory Acceptance of PBPK

Supplement Article

ACCP

Application of PBPK Modeling and Simulation for Regulatory Decision Making and Its Impact on US Prescribing Information: An Update on the 2018-2019 Submissions to the US FDA's Office of Clinical Pharmacology

The Journal of Clinical Pharmacology 2020, 60(S1) S160–S178
Published 2020. This article is a U.S. Government work and is in the public domain in the USA
DOI: 10.1002/jcph.1767

Xinyuan Zhang, PhD, Yuching Yang, PhD, Manuela Grimstein, PhD, Jianghong Fan, PhD, Joseph A. Grillo, PharmD, Shiew-Mei Huang, PhD, Hao Zhu, PhD, and Yaning Wang, PhD

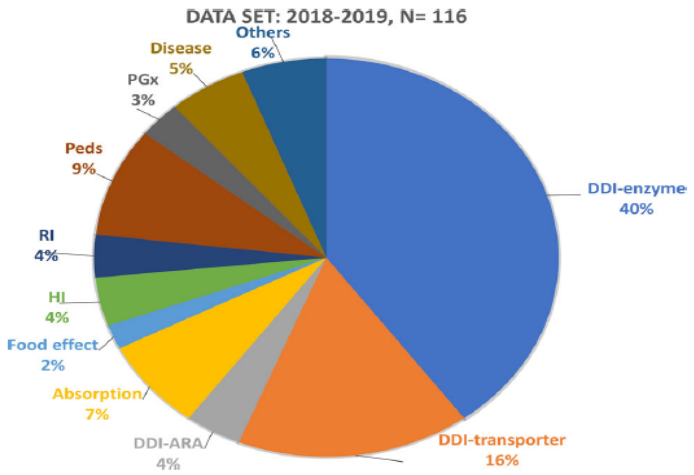


Figure 3. Distribution of physiologically based pharmacokinetic submissions by application areas (2018-2019). DDI-ARA, acid-reducing agent-mediated drug-drug interaction; DDI-enzyme, enzyme-mediated drug-drug interaction; DDI-transporter, transporter-mediated drug-drug interaction; HI, hepatic impairment; peds, pediatrics; PGx, pharmacogenomics; RI, renal impairment.

Zhang et al. J Clin Pharm 2020

Commentary

Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs

Fang Wu,[1,2,9] Heta Shah,[3] Min Li,[1] Peng Duan,[3] Ping Zhao,[4,5] Sandra Suarez,[3] Kimberly Raines,[1] Yang Zhao,[1,6] Meng Wang,[1,7] Ho-pi Lin,[1] John Duan,[3] Lawrence Yu,[8] and Paul Seo[1,9]

Received 16 October 2020; accepted 1 February 2021

Abstract. Physiologically based pharmacokinetic (PBPK) absorption modeling and simulation is increasingly used as a tool in drug product development, not only in support of clinical pharmacology applications (e.g., drug-drug interaction, dose selection) but also from quality perspective, enhancing drug product understanding. This report provides a summary of the status and the application of PBPK absorption modeling and simulation in new drug application (NDA) submissions to the U.S. Food and Drug Administration to support drug product quality (e.g., clinically relevant dissolution specifications, active pharmaceutical ingredient (API) particle size distribution specifications). During the 10 years from 2008 to 2018, a total of 24 NDA submissions included the use of PBPK absorption modeling and simulations for biopharmaceutics-related assessment. In these submissions,

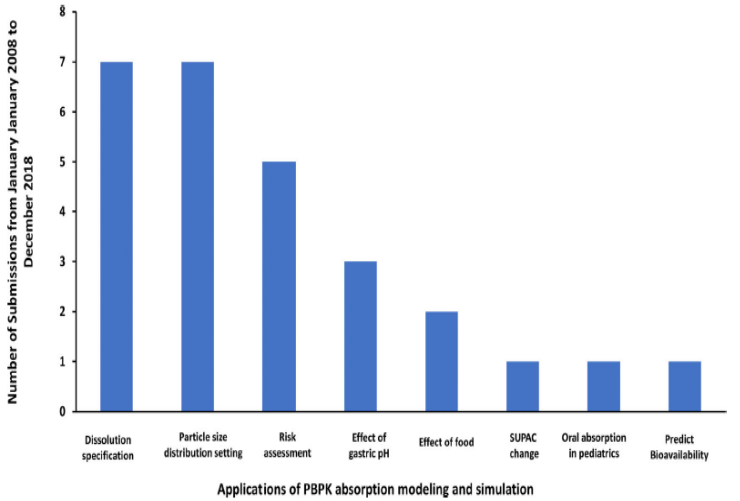


Fig. 2. Applications of PBPK absorption modeling and simulations in the new drug applications submissions*. Abbreviations: SUPAC, scale-up and post-approval changes. *Note that in some cases, the same model was used for multiple purposes, e.g., setting of both particle size specification and dissolution acceptance criteria

Wu et al. AAPS J 2021

PBBM/PBPK Modeling to Support Regulatory Interaction New Guidance Documents!

Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

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

2018

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

OCT 2020

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

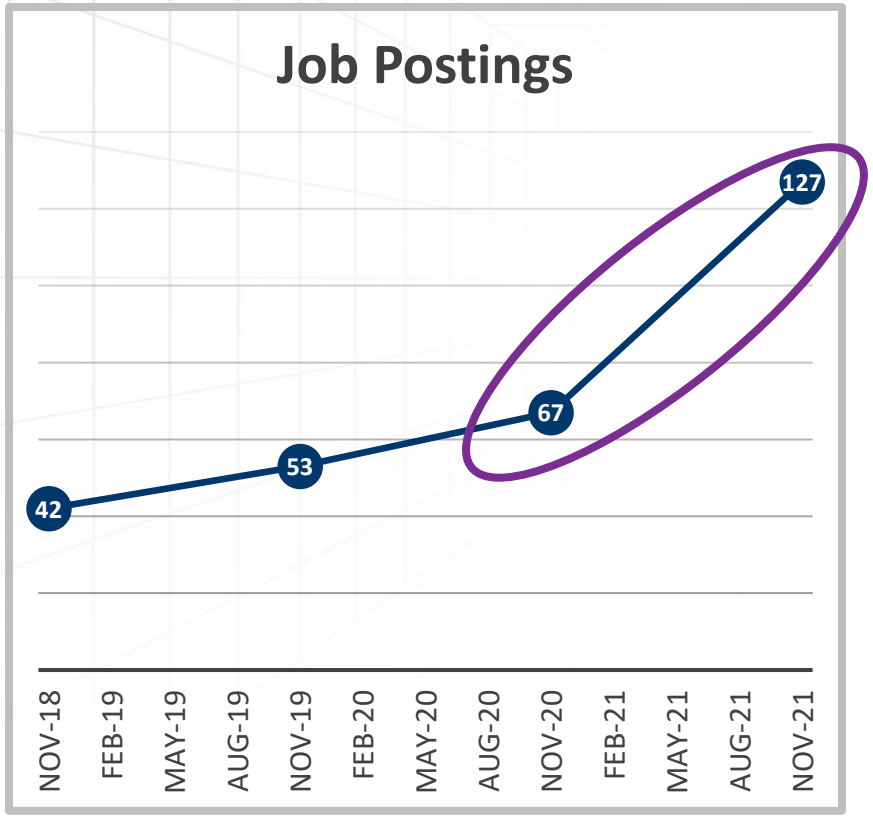
- **Physiologically based PK simulations:** In conjunction with the assessment framework outlined in Figure 1, physiologically based PK (PBPK) simulations can sometimes be used to further assess the potential for pH-dependent DDIs. PBPK approaches can also be useful to inform clinical study designs. 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.

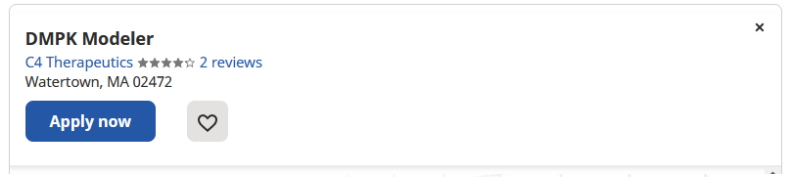
DRAFT GUIDANCE

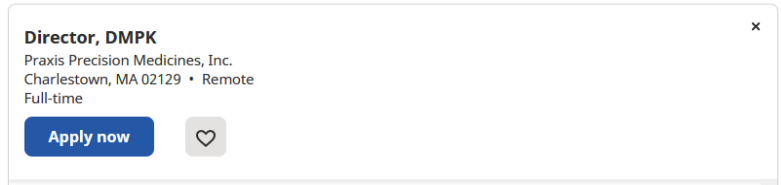
https://www.fda.gov/media/144026/download

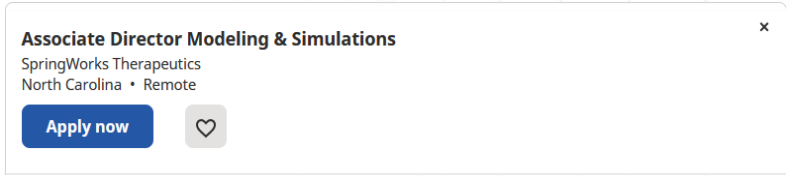
NOV 2020

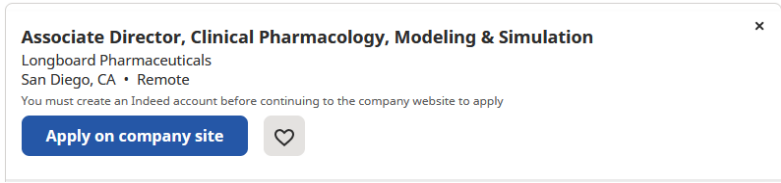
What a Great Time to be a PBPK Modeler!











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Concluding Remarks

PBPK/PBBM model development can be initiated at any stage of product development

- Irrespective of the extent of data in-hand

Earlier the better

- More time for understanding the compound and drug product
- More time for model refinement
- Readiness for regulatory applications
  - Safe space: API PSD, Dissolution etc.
  - IVIVC
  - Bio-waivers
  - SUPAC

Acknowledgements

- Simulations Plus, Inc.
  - Becky Graves
    - Associate Director, Simulation Studies Team
  - Jim Mullin
    - Sr. Principal Scientist, Simulations Technologies Group, and Product Manager of DDDPlus™ and MembranePlus™
  - Jennifer Dilts
    - Operations Specialist
  - John DiBella
    - President, Simulations Plus

Thank you ☺

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