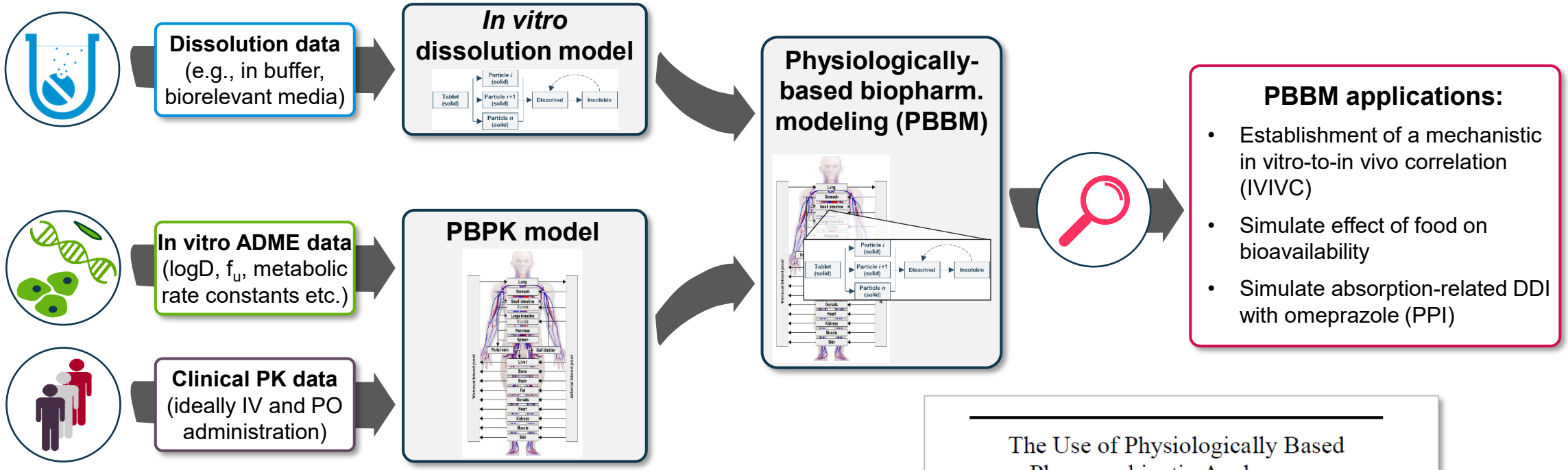
Bridging In Vitro Dissolution and In Vivo Pharmacokinetics: Application of a Novel PBBM Workflow to Vericiguat

Paul Vrenken & André Dallmann

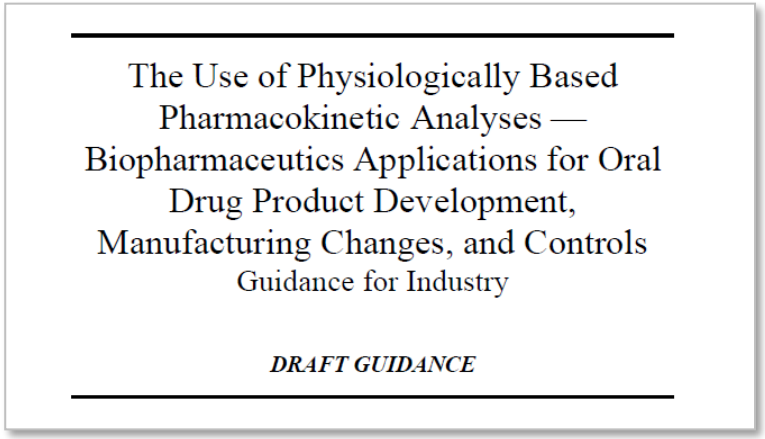
OSP Community Conference, September 29, 2025

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 955756.

Physiologically-based biopharmaceutics modeling (PBBM): PBPK modeling with a focus on biopharmaceutics



- Approach encouraged by the FDA (2020)


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

DRAFT GUIDANCE

Abbreviations: ADME: absorption, distribution, metabolism, and excretion; fu: fraction unbound; PK: Pharmacokinetics

Generic PBBM framework implemented in OSP

GitHub

Development of 3 open-source tools for seamless PBBM simulations:

Solubility toolbox

– Interactive tool to derive relevant parameters controlling drug solubilization from in vitro data –

Input: Solubility measured in various media (buffer, biorelevant media etc.) as Excel file

Output: Visual predictive checks and fitted/calculated parameter values for describing:

- Drug solubility vs. pH profile
- Water:micelle partitioning for neutral and ionized drug species

In vitro dissolution module

MoBi®

– Versatile model for release kinetics that enables bridging between various in vitro test conditions –

Extends the particle dissolution model implemented in PK-Sim® by the following features:

- semi-mechanistic description of the aqueous diffusion layer
- integration of micellar solubilization

PBPK with new dissolution features

PK-Sim®

– Updated human GI tract and inclusion of novel dissolution equation for better PBBM capabilities with PK-Sim® –

Updates and adds novel GI tract parameters to PK-Sim®, e.g.:

- Luminal bile salt concentrations
- Population variability on luminal pH

Describes stomach pH as a function of hydrogen dilution through water intake

Adds new dissolution model to PK-Sim®

→ **seamless linking of PBPK with in vitro dissolution simulated in MoBi®**

https://github.com/Open-Systems-Pharmacology/Oral-PBBM-Workflow

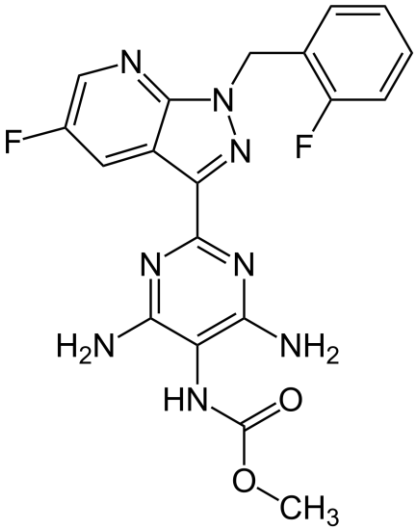
Case study: Vericiguat (Verquvo®)

- Soluble guanylate cyclase (sGC) stimulator
  - Indication: heart failure with reduced ejection fraction (<45%)
  - Dose strengths: 2.5, 5 and 10 mg
- Poorly soluble, highly permeable (**BCS class II**)
  - *In vitro* solubility and dissolution data available
  - *In vitro* data suggests **low risk of intestinal precipitation**
- **Pharmacokinetics**: Affected by prandial state and gastric pH elevating agents (e.g., proton pump inhibitor: Omeprazole)

Factor	Effect on AUC	Effect on C_{max}
Food effect (10 mg dose)[b]	↑ +44%	↑ +41%
Omeprazole intake[c]	↓ -32%	↓ -49%

Modeling aim: Evaluate PBBM workflow by comparing observed with predicted vericiguat pharmacokinetics

- Fasted state, following a meal (fed state) or PPI treated state (omeprazole)



Parameter, unit	Value	Reference
Molecular weight, g/mol	426.39	[a]
Lipophilicity, log units	2.99	[a]
pK_a (base)	4.68	[a]
Reference solubility (at pH 6.8), mg/L	1.9	Measured

a) Frechen et al., *CPT:PSP, 13, 2024*
b) Becker et al., *AAPS Open*, *8, 2022*
c) Boettcher et al., *Eur. J. Clin. Pharmacol.*, 77, 2021

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Solubility toolbox

Understanding the effect of pH on solubility
(Henderson-Hasselbalch equation)

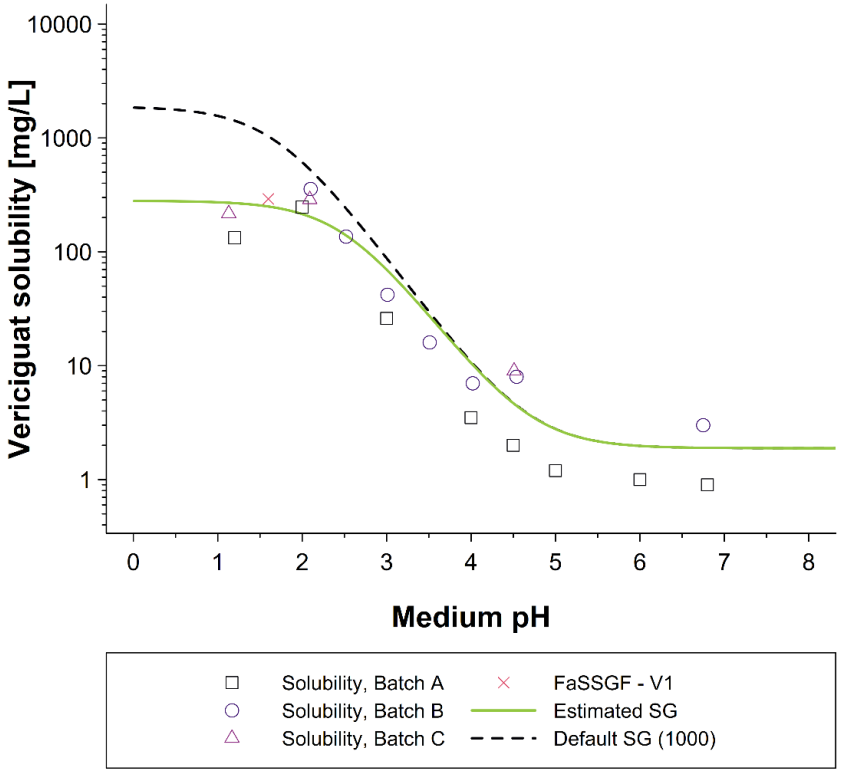
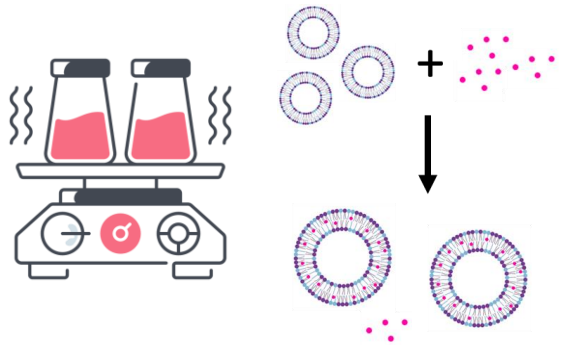


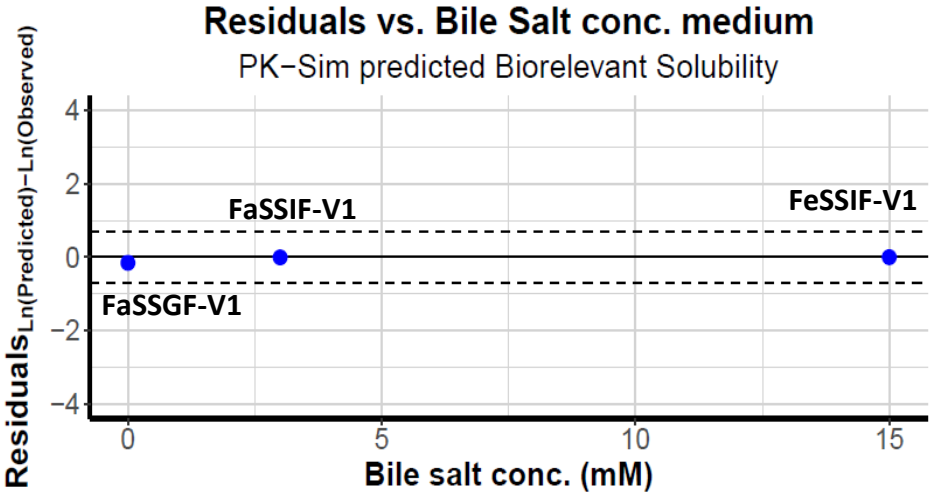
Figure adapted from: Vrenken et al. Eur J Pharm Sci. 212, 2025



$$S_{br} = \left([Bile] \times \frac{S_0}{[H_2O]} \times K_{m:w,neutral} + S_0\right) + \left([Bile] \times \frac{S_i}{[H_2O]} \times K_{m:w,ionized} + S_i\right)$$

Sugano. Exp Opinion Drug Met & Tox. 5, 2009

Understanding the effect of bile salts on solubility



Abbreviations: SG: Solubility gain per charge; FaSSGF-V1: fasted state simulating gastric fluid version 1; FaSSIF-V1: fasted state simulating intestinal fluid version 1; FeSSIF-V1: fed state simulating intestinal fluid version 1

Implemented versatile Particle Dissolution equation

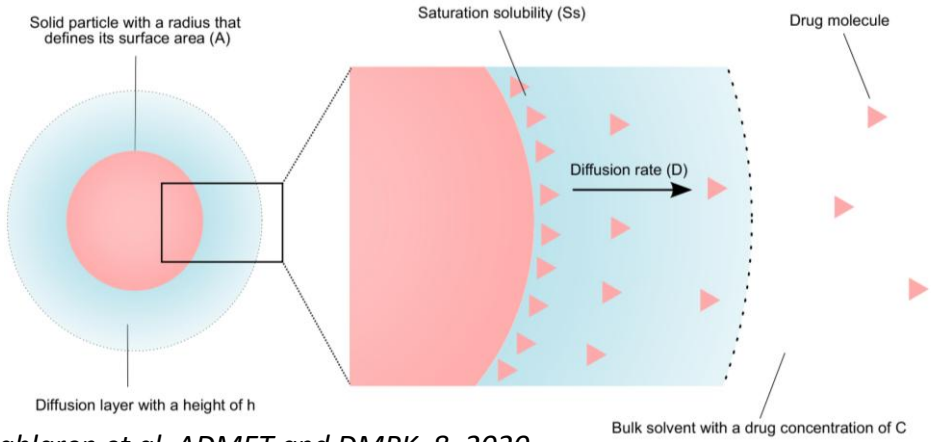
Sub-models can be switched on/off based on drug, available data and application

In vitro dissolution module MoBi®

$$\frac{dm_{solid}}{dt} = -A * \left(\frac{D_u}{h_u} * \left(S_{u,surf} - C_u \right) + \frac{D_b}{h_b} * \left(S_{b,surf} - C_b \right) \right) * \Psi$$

Gamsiz et al., Pharm. Res., 27, 2010

u = unbound, b = micelle bound



Dahlgren et al. ADMET and DMPK, 8, 2020

Surface Area (*A*)

Particle Size
(Monodispersed or Distribution)

$$A = 4\pi r_t^2 N_0$$

$$N_0 = \frac{Amount_{bin,0}}{\left(\frac{rho}{MW} \times \frac{4}{3} \pi r_{bin,0}^3 \right)}$$

Solubility (*S*)

OSP solubility toolbox:
- SG estimation tool for ionizable drugs
- Mechanistic bile salt micelle model ($S_{b,surf}$)
- Surface pH model (manual calculation)

Diffusion coefficient (*D*)

Molecularly dissolved unbound drug (u) and bile salt micelle bound (b)

- D_u: Measured value or OSP empirical eq.
- D_b: Stokes-Einstein eq.

Diff. layer thickness (*h*)

Constant h:
- Default: 30 µm

Hintz-Johnson model:
- h = particle radius (Max h = 30 µm)

Hydrodynamic model:
- (semi)Mechanistic
- *In vitro* conditions

Surface integration factor (Ψ)
- Accounts for processes occurring at the particle surface that slow the precipitation rate

Sjögren et al., Eur. J. Pharm. Sci., 4, 2013

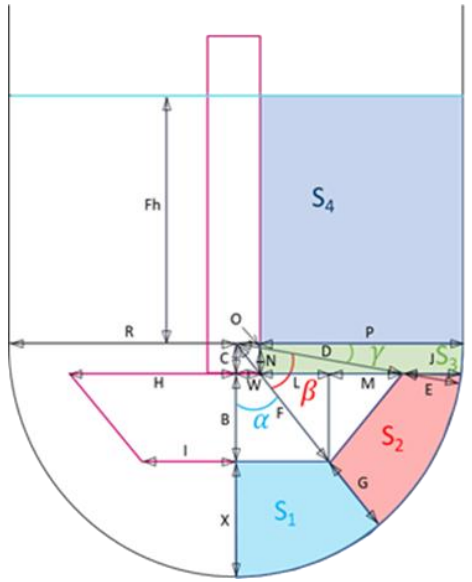
In vitro dissolution module MoBi®

Hydrodynamic Modeling in USP2 Vessel

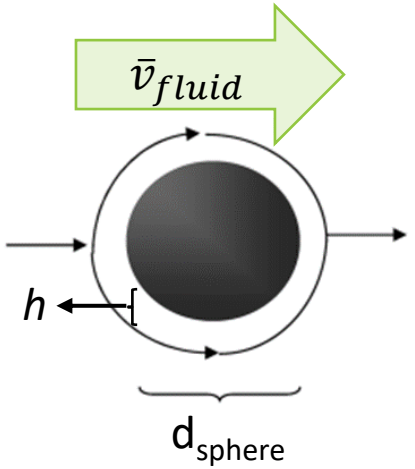
- (Semi-)Mechanistic model to capture fluid motion and shear effects, to calculate Reynolds number (*Re*)

Assumptions and Validation

- Vessel divided into velocity zones; velocities estimated from paddle geometry and rotational speed
- Approach validated against CFD simulations and experimental data



Pepin et al. J Pharm Sci. 111, 2022



Surface area of drug particles
(depends on drug product properties)

Diffusion coefficient of free drug
(drug- and medium-specific)

Diffusion coefficient of micelle-bound drug
(micelle- and medium-specific)

Surface integration factor
(depends on drug product and medium properties)

$$\frac{dm_{solid}}{dt} = -A \times \left(\frac{D_u}{h_u} \times (S_u - C_u) + \frac{D_b}{h_b} \times (S_{br} - C_b) \right) \times \Psi$$

Diffusion layer of free and micelle-bound drug
(depends on agitation rate and medium viscosity)

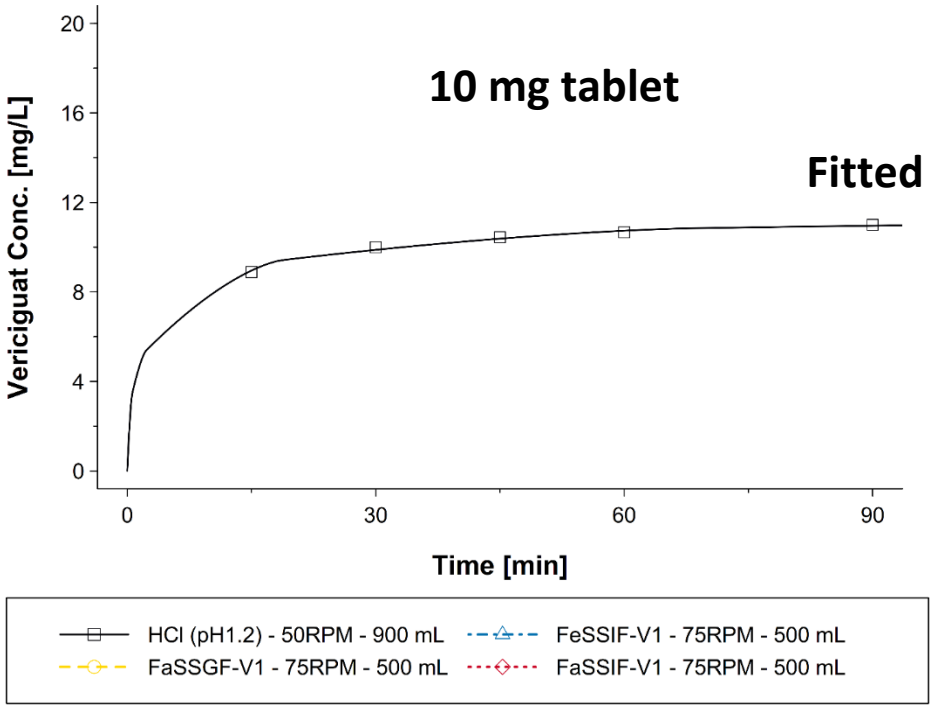
Solubility of free and micelle-bound drug
(depends on medium pH, buffer capacity & micelles)

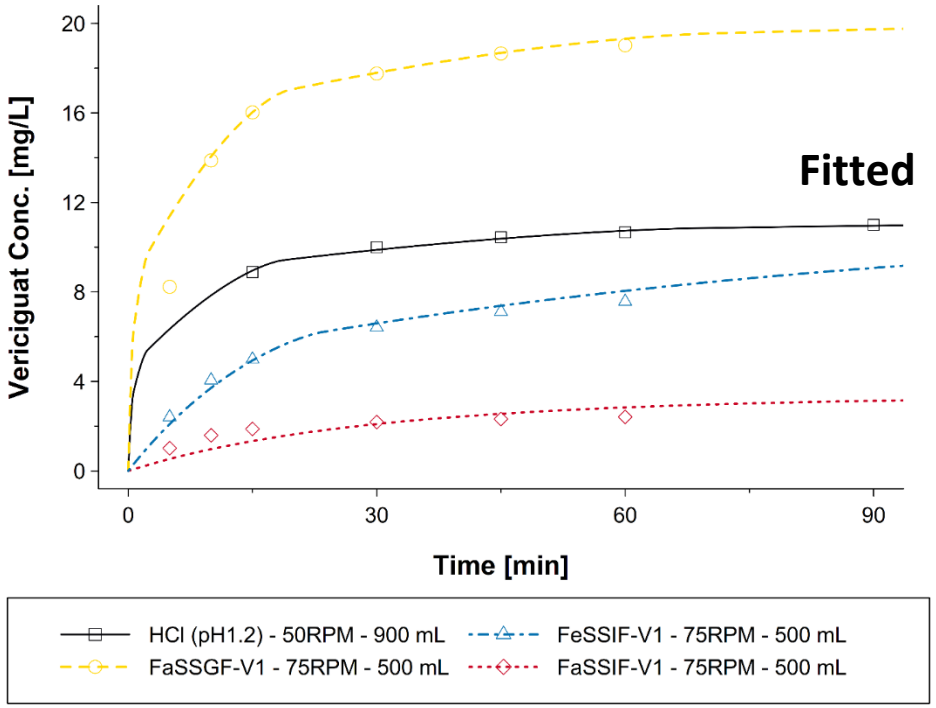
In vitro dissolution module MoBi®

Understanding dissolution kinetics in vitro
(Novel dissolution model)

Predicting dissolution at different conditions when changing:

- Medium volume
- Medium pH
- Buffer capacity
- Medium viscosity
- Agitation rate
- Micelle conc.



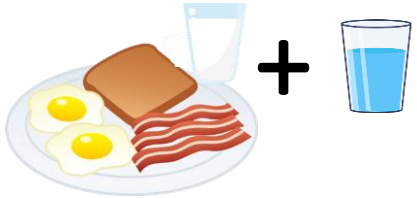


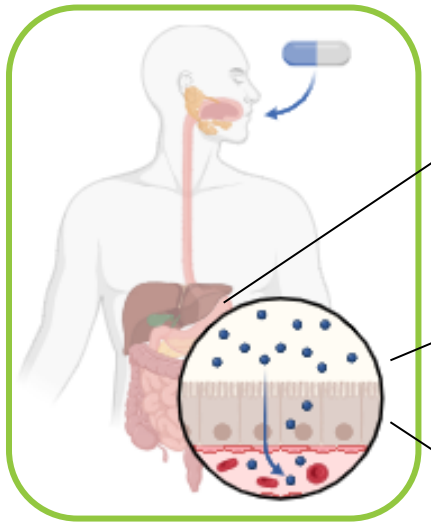
Figures adapted from: Vrenken et al. Eur J Pharm Sci. 212, 2025

Abbreviations: HCl: hydrochloride; FaSSGF-V1: fasted state simulating gastric fluid version 1; FaSSIF-V1: fasted state simulating intestinal fluid version 1; FeSSIF-V1: fed state simulating intestinal fluid version 1; RPM: rotations per minute

PBPK with new dissolution features

PK-Sim®





Gastric pH
- Population Variability
- Dynamic

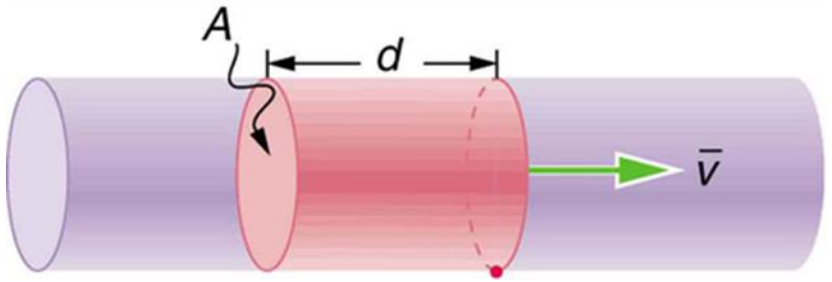
Bile salt concentrations
- Population Variability
- Dynamic (fed)

Hydrodynamic model options:
- Simplified hydrodynamic model
  - Assuming laminar flow
  - Inbuild liquid transfer rate
- Hintz-Johnson model (available)

$$h_u = \frac{2r}{Sh} \longrightarrow \frac{h_b}{h_u} = \sqrt[3]{\frac{D_b}{D_u}}$$

$$Sh = 2 + 0.6Re_p^{1/2}Sc^{1/3}$$

$$Re_p = \frac{2r \times \bar{v}_{fluid}}{\vartheta} \qquad Sc = \frac{\vartheta}{D_u}$$



r = particle radius, ϑ = kinematic viscosity, *u* = unbound, *b* = bound, $\bar{v}_{fluid}$ = Average fluid velocity, $r_{Average}$ = intestinal radius

Repurposing a qualified vericiguat PBPK model for PBBM

Received: 13 June 2023 | Revised: 21 September 2023 | Accepted: 25 September 2023

DOI: 10.1002/psp4.13059

ARTICLE

Applied physiologically-based pharmacokinetic modeling to assess uridine diphosphate-glucuronosyltransferase-mediated drug–drug interactions for Vericiguat

Sebastian Frechen[1] | Ibrahim Ince[1] | André Dallmann[1] | Michael Gerisch[2] | Natalia A. Jungmann[2] | Corina Becker[3] | Maximilian Lobmeyer[3] | Maria E. Trujillo[4] | Shiyao Xu[4] | Rolf Burghaus[1] | Michaela Meyer[1]

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to the FDA's information requests (IRs) submitted on September 30, 2020, October 13, 2020, and November 18, 2020 and concluded the following:

- The vericiguat PBPK model is adequate to predict the vericiguat PK profiles following a single dose administration (0.5, 1, 2.5, 5, 7.5, 10 and 15 mg) and multiple does administration (1.5, 5 and 10 mg, qd and 5 mg bid) in healthy subjects.

4.3.2 Applicant's PBPK Modeling Effort

PBPK software

PK-Sim V7.1 and MoBi V7.1 (Open Systems Pharmacology) were used by the Applicant to develop the PBPK models and DDI predictions. The reviewer used the PK-Sim V 9.0 for analyses.

Model development

Vericiguat and M-1

Absorption

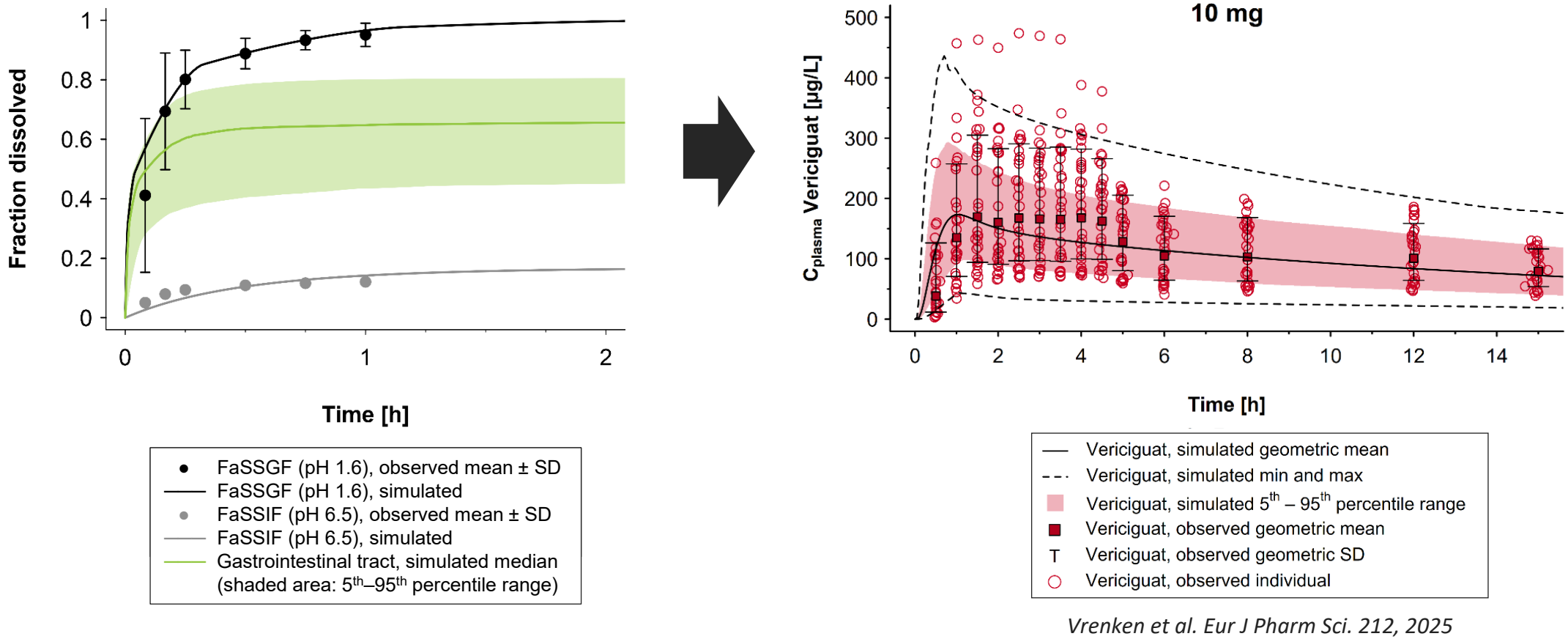
A human whole body PBPK model was developed to characterize the PK of vericiguat and its major metabolite M-1 in plasma, urine and feces. Weibull cumulative distribution functions were fitted to the clinical observed PK data to obtain the dissolution parameters "dissolution time (50% dissolved" and the "dissolution shape" of the tablet formulations for 1.25, 2.5, 5 and 10 mg tablets. Intestinal permeability (4.11E-5 cm/min and 5.78E-7 cm/min) and organ permeability (4.48E-3 cm/min and 4.99E-6 cm/min) were estimated in PK-Sim for vericiguat and M-1 based on the physicochemical properties, respectively.

Exchanging the empirical dissolution module with the PBBM dissolution module required refitting of intestinal permeability; all other parameters were kept unchanged (→ PBBM not qualified for DDI!)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214377Orig1s000IntegratedR.pdf

Fasted state: PBBM links *in vitro* dissolution to *in vivo* PK

10 mg tablet



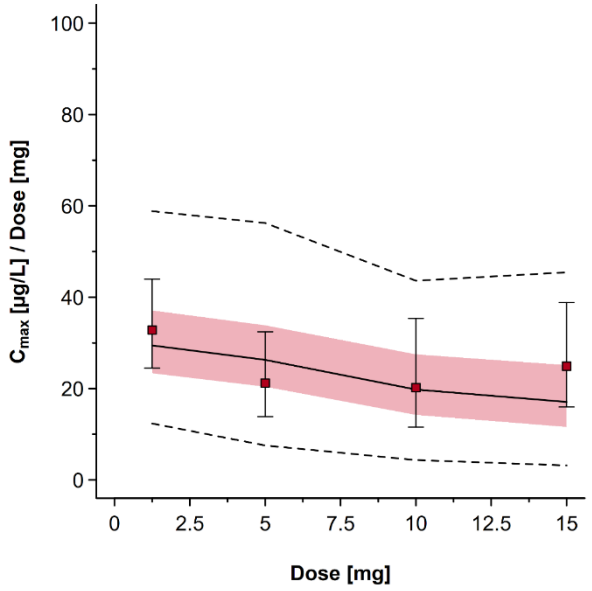
Vrenken et al. Eur J Pharm Sci. 212, 2025

P-PSD approach translates well to *in vivo* fasted state PK

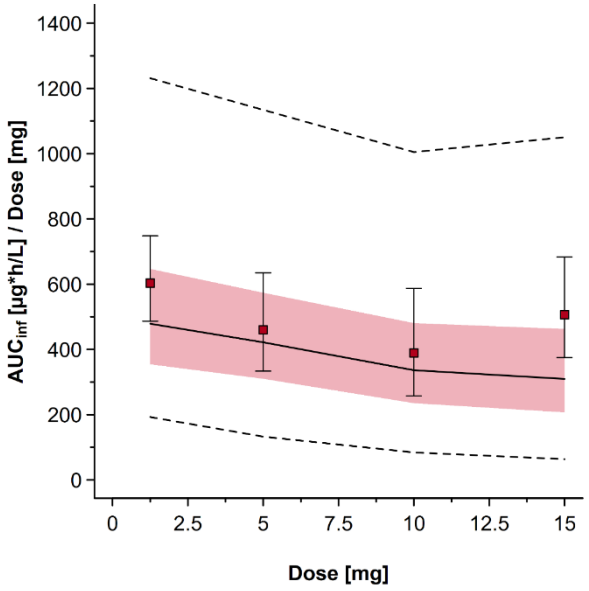
No pronounced dose non-linearity observed or predicted

As 1.25, 5 or 10 mg tablet:

Dose normalized C_{max}

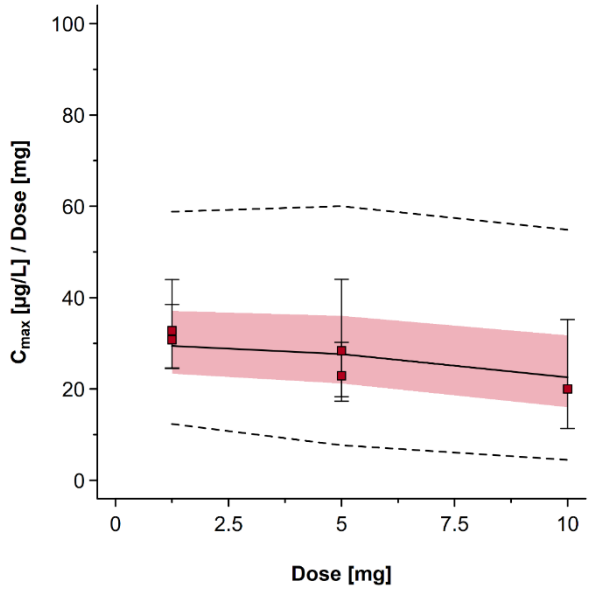


Dose normalized AUC

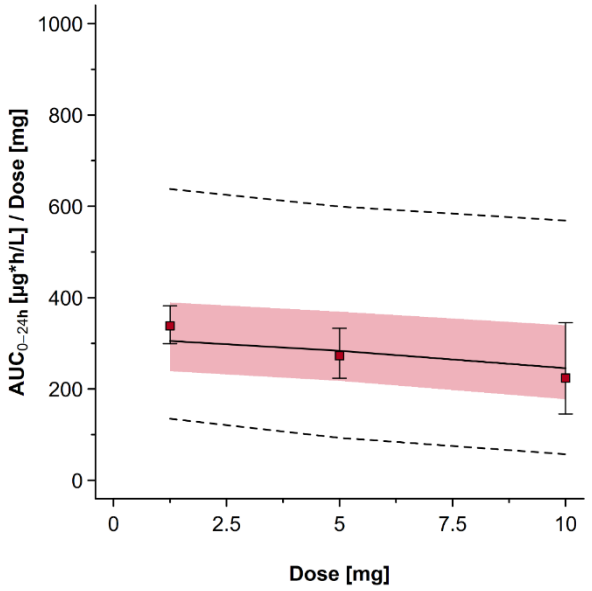


As 1.25 mg tablet(s):

Dose normalized C_{max}

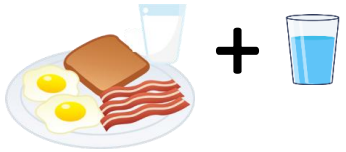


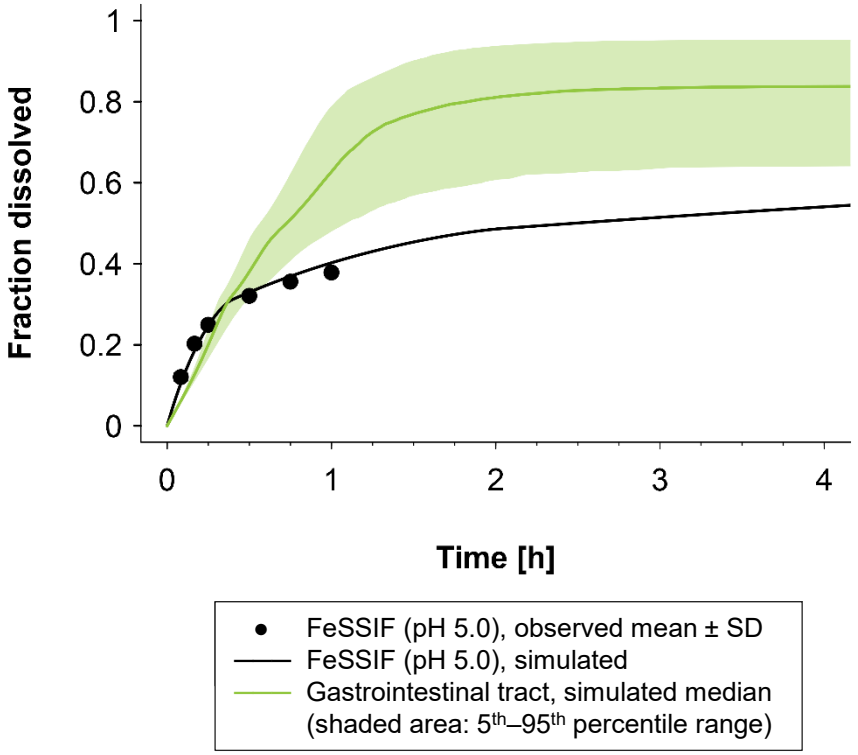
Dose normalized AUC

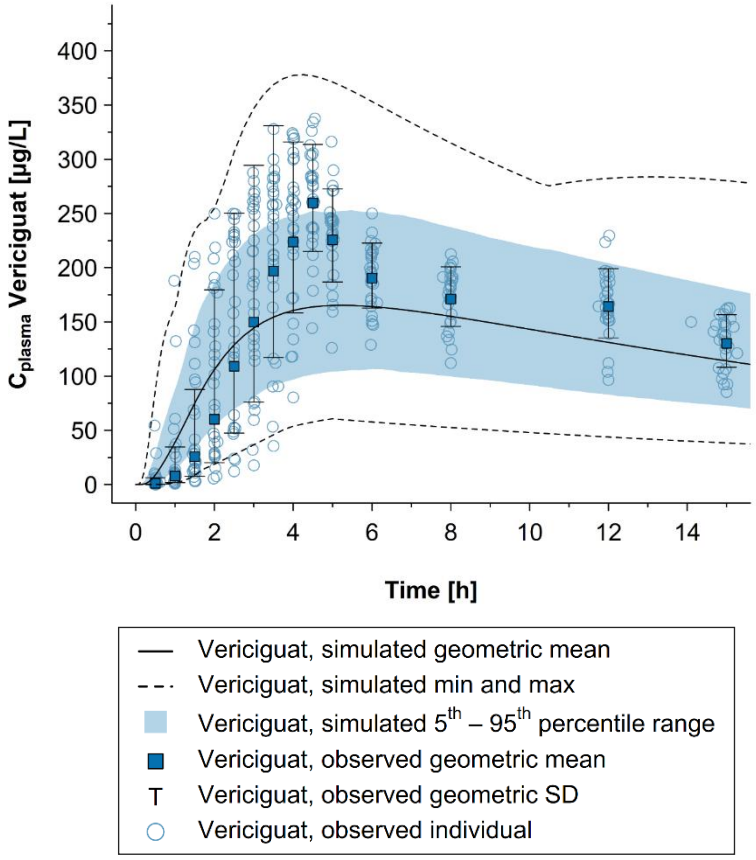


Vrenken et al. Eur J Pharm Sci. 212, 2025

Fed state: Delay in t_{max} captured, C_{max} underestimated





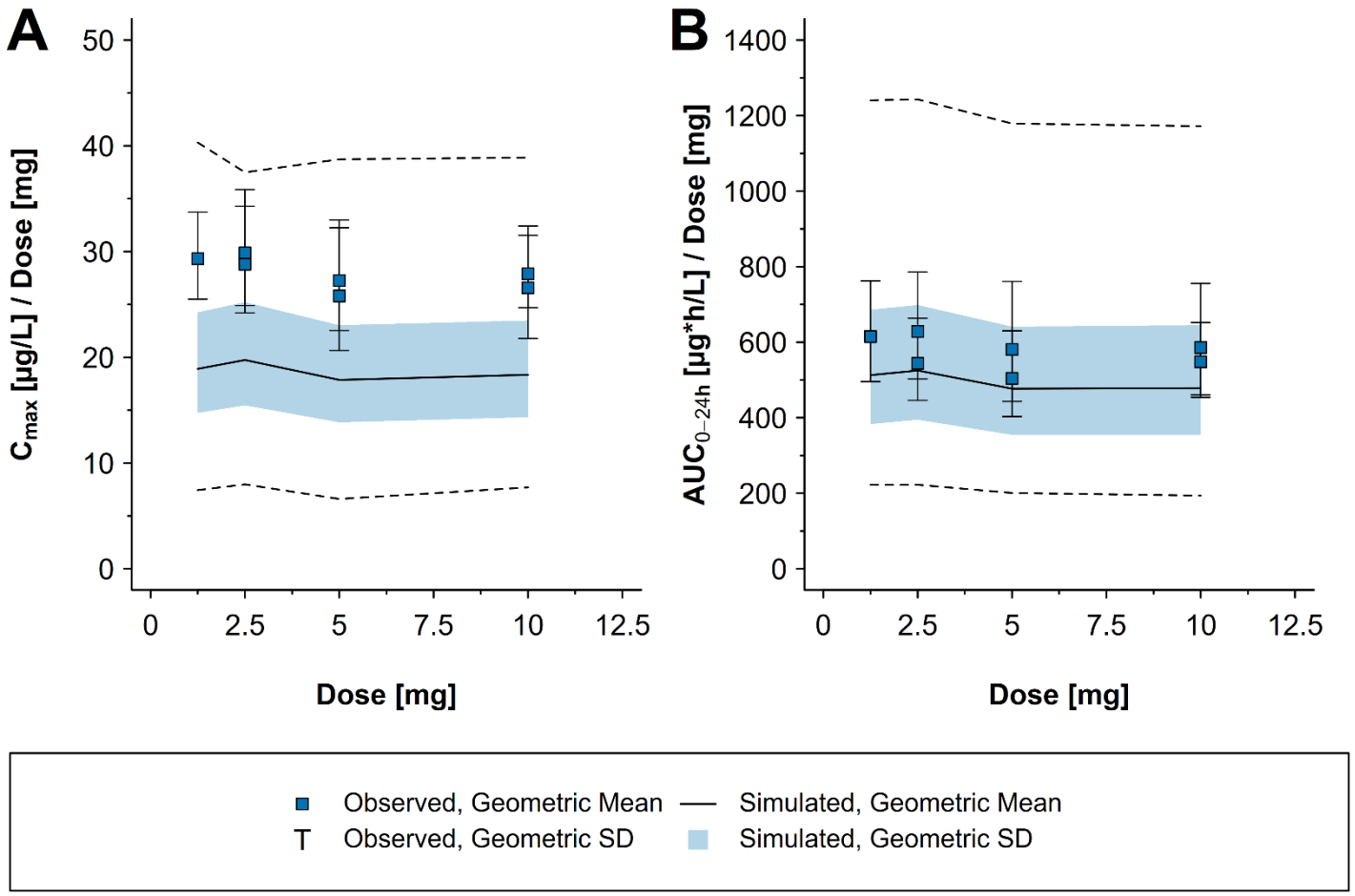


Vrenken et al. Eur J Pharm Sci. 212, 2025

Food effect on	Observed[a]	Simulated
AUC_{inf}	+44%	+38%
C_{max}	+41%	−15%

[a] *Becker et al., AAPS Open, 8, 2022*

AUC well captured, but C_{max} underestimated across doses



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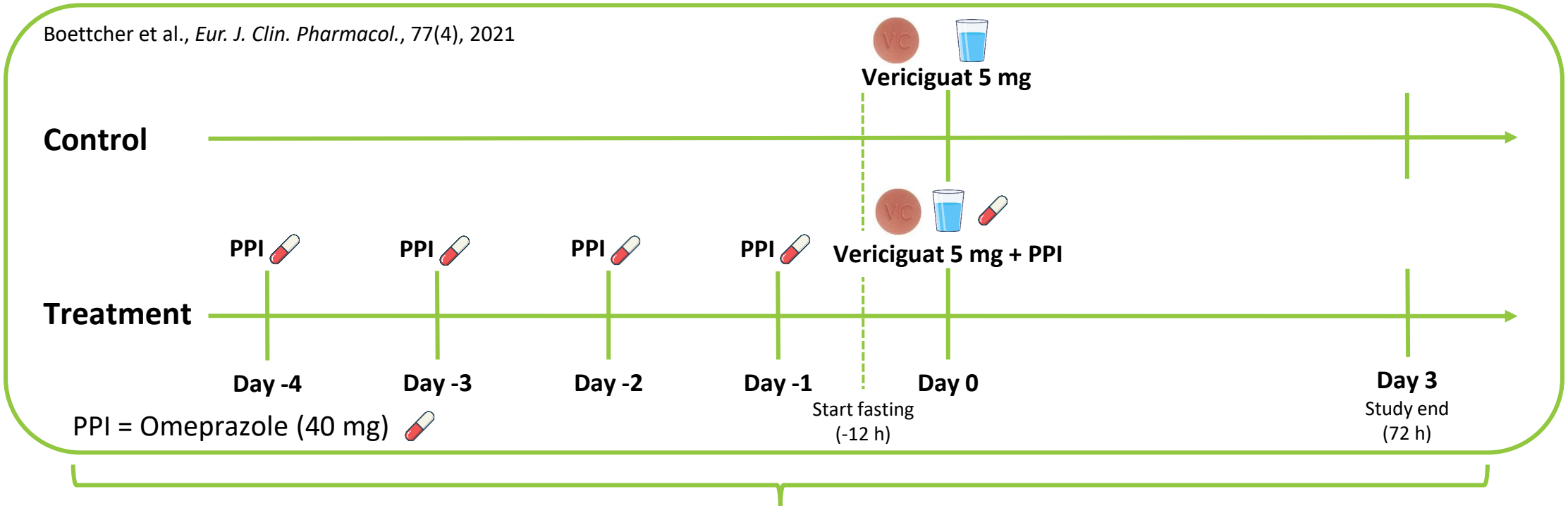
Interaction with omeprazole, a proton pump inhibitor (PPI)



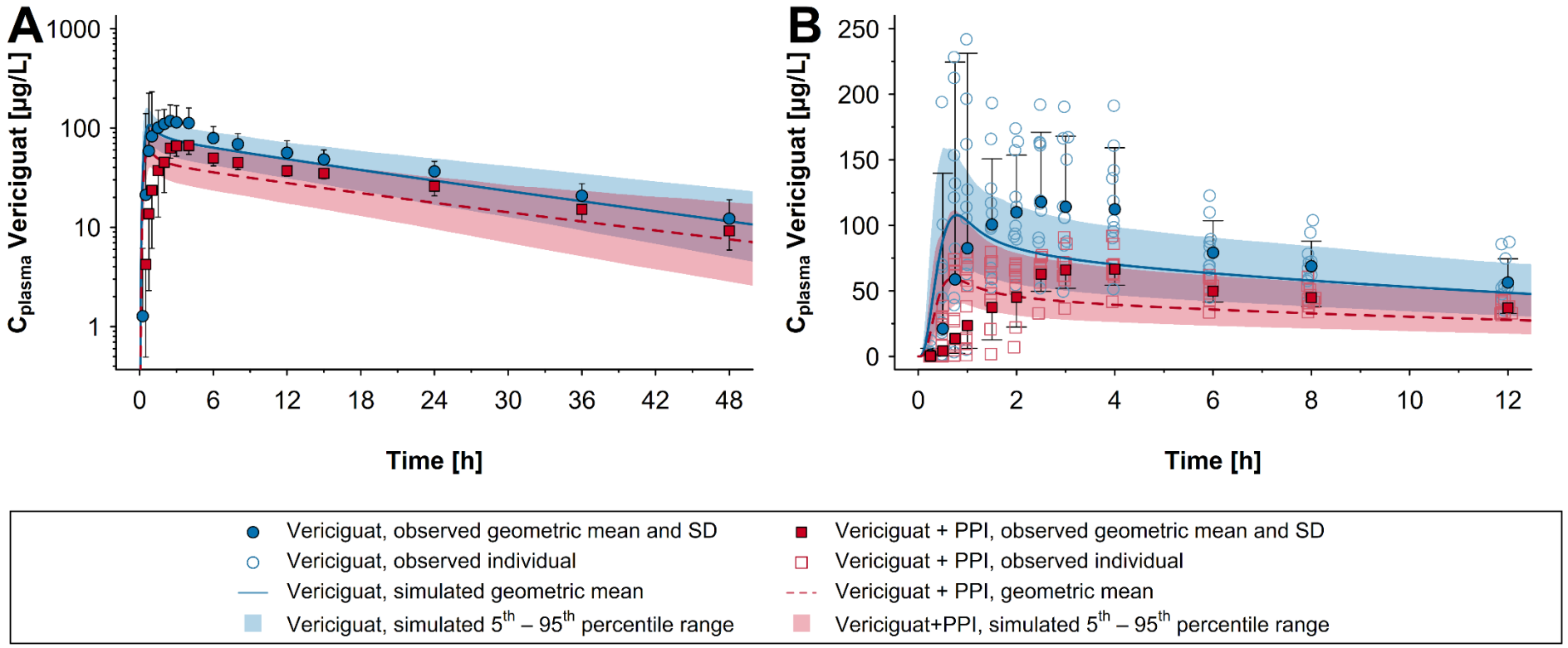
Translation of the PPI effect (PBBM):

- Gastric pH after similar treatments: 4.6 ± 1.6 (n = 76)

  Kirchheiner et al., Eur. J. Clin. Pharmacol., 65(1), 2009

- Created a “PPI population” in PK-Sim® (n = 1000)

PPI interaction effect captured, but t_{max} underestimated



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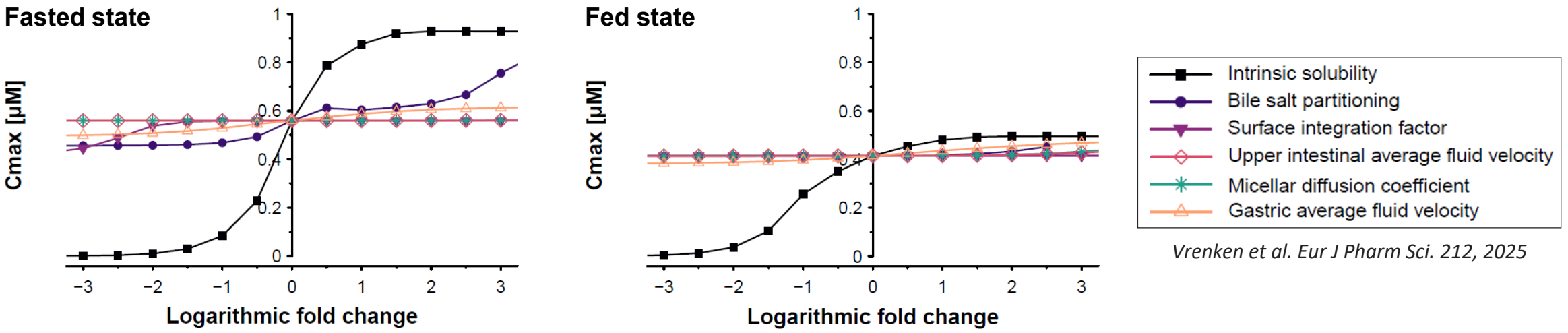
	Observed	Predicted	Ratio (Pred/Obs)
AUC	−32%	−39%	1.21
C_{max}	−49%	−47%	0.97

Insights from sensitivity analyses



Vrenken et al. Eur J Pharm Sci. 212, 2025

- **Shared sensitivity:** Cmax and AUC were both influenced by the same set of tested parameters.
- In vitro-derived parameters, specifically **intrinsic solubility** and **bile salt partitioning**, were the most sensitive inputs.
- **Fluid dynamics** in the gastrointestinal tract had little influence on the simulation results.
- **Cmax underestimation in fed state** remains unexplained: No parameter could be identified with a selective impact on fed state Cmax.

Conclusions and Outlook

- **Bottom-up approach** linking vericiguat's *in vitro* solubility and dissolution kinetics to *in vivo* drug exposure
- Predictive PBBM-based IVIVC can be applied to:
  - Develop biopredictive dissolution methods that correlate with in vivo performance
  - Support formulation optimization, selection, and bridging by simulating clinical performance of candidate formulations
  - Conduct virtual bioequivalence trials
  - Assess interaction risks with acid-reducing agents and proton pump inhibitors
  - Provide support for regulatory applications, including biowaivers for lower strengths and modifications in manufacturing processes
- More case studies, including non-bioequivalent formulations, are needed to build confidence
- **Future improvements:**
  - Solving the **fed state challenge** (Cmax underestimation)
  - Extend solubility models to include **multiple solid states**, e.g., amorphous and salt forms
  - Enhance precipitation models: **particle regrowth vs. nucleation** or "particle birth" models
  - Improve methods for estimating **intestinal permeability** based on, e.g., in vitro permeability measurements

Article series on the PBBM framework:

Vrenken P, Vertzoni M, Frechen S, Solodenko J, Meyer M, Muenster U, Dallmann A. Development of a novel physiologically based biopharmaceutics modeling (PBBM) framework using the open systems pharmacology suite, part 1: in vitro modeling of vericiguat. *Eur J Pharm Sci.* 2025 Sep 1;212:107164. doi: 10.1016/j.ejps.2025.107164. Epub 2025 Jun 10. PMID: 40505839.

Vrenken P, Vertzoni M, Frechen S, Solodenko J, Meyer M, Muenster U, Dallmann A. Development of a novel physiologically based biopharmaceutics modeling (PBBM) framework using the open systems pharmacology suite, part 2: in vivo pharmacokinetic modeling of vericiguat. *Eur J Pharm Sci*. 2025 Sep 1;212:107189. doi: 10.1016/j.ejps.2025.107189. Epub 2025 Jul 2. PMID: 40615096.

Use the PBBM framework via OSP GitHub:

https://github.com/Open-Systems-Pharmacology/Oral-PBBM-Workflow

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- Juri Solodenko (Bayer AG)
- Michaela Meyer (Bayer AG)
- Uwe Muenster (Bayer AG)

Thank you!

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