Best practices in model development: input of solubility, supersaturation, precipitation and permeability

Current state and future expectations of Translational Modeling strategies to support drug product development, manufacturing changes and controls

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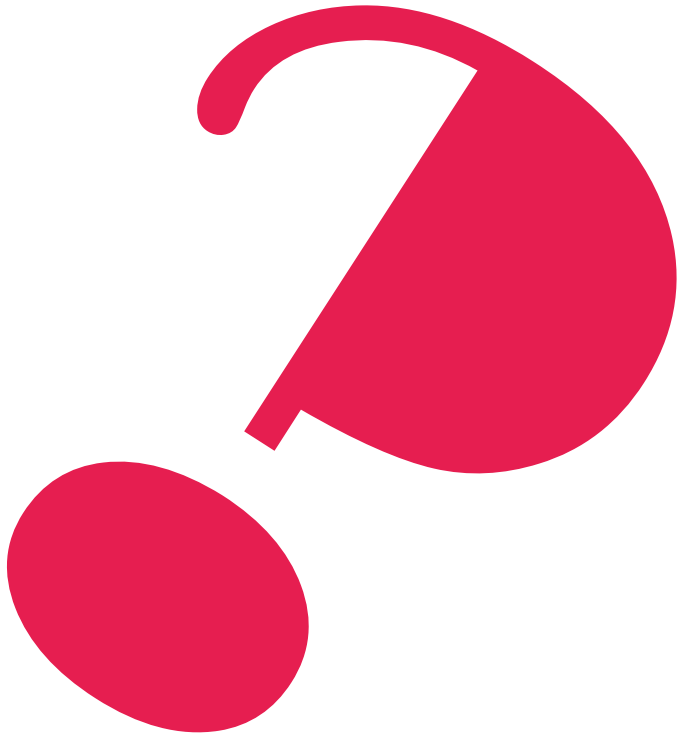

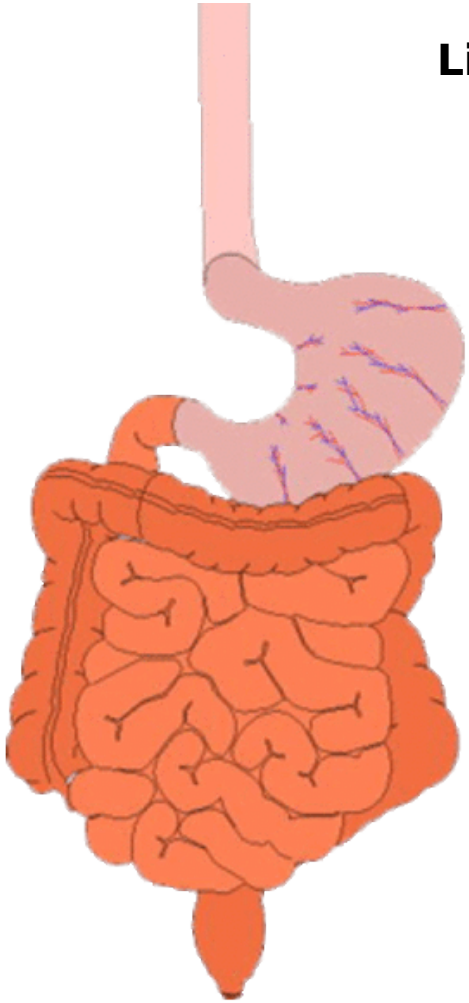

Liberation and dissolution

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Absorption

↓

Distribution

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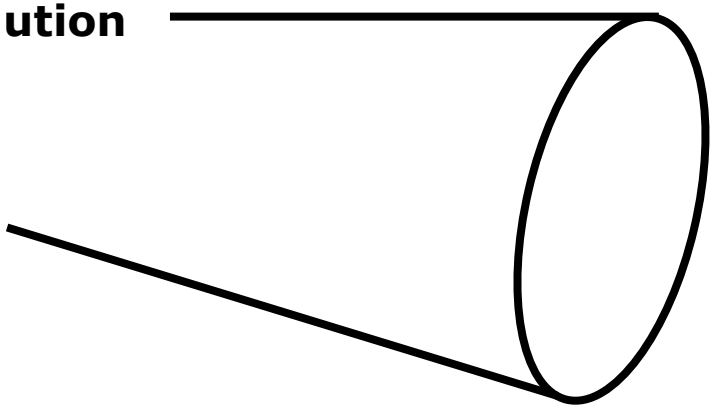
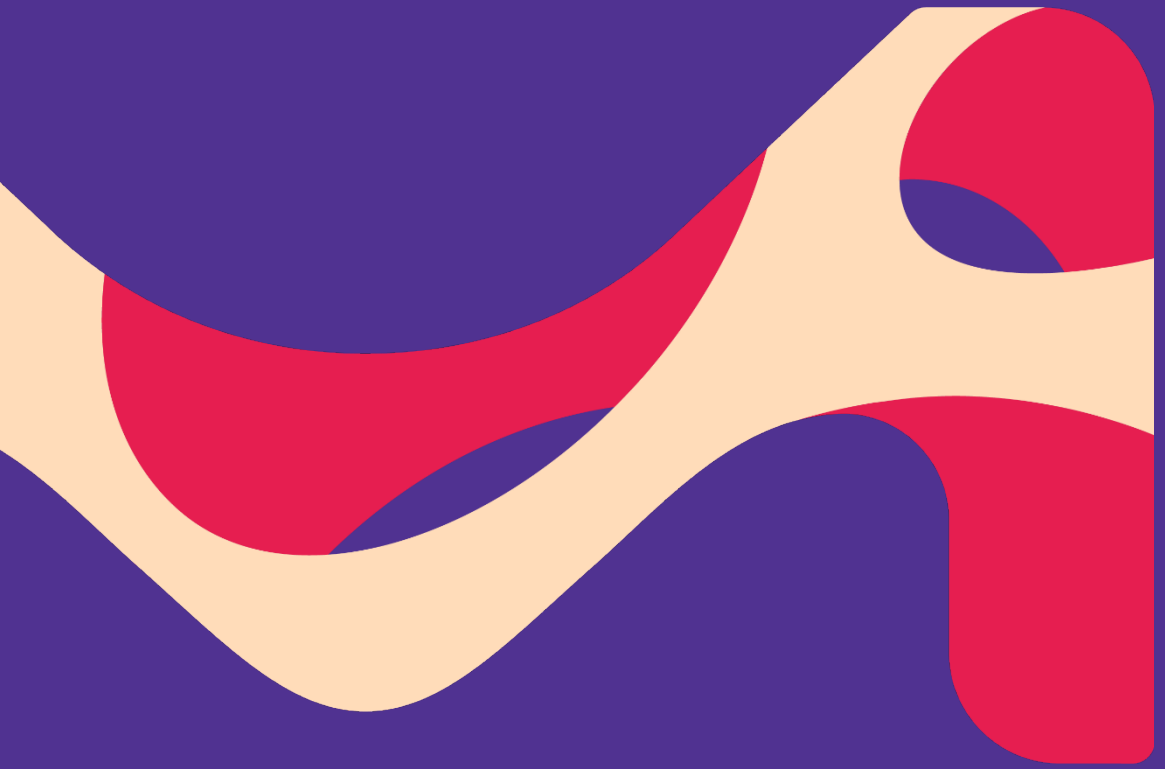
Metabolism

↓

Excretion



- **Solubility**
- **Supersaturation**
- **Precipitation**
- **Permeability**

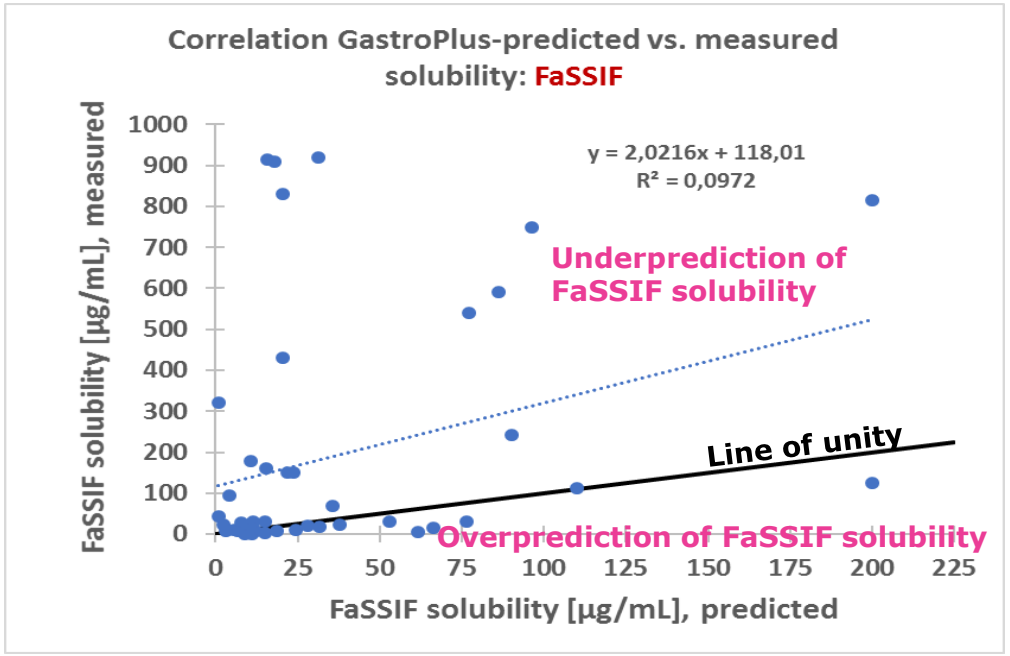


01

Solubility

Best practice: Solubility

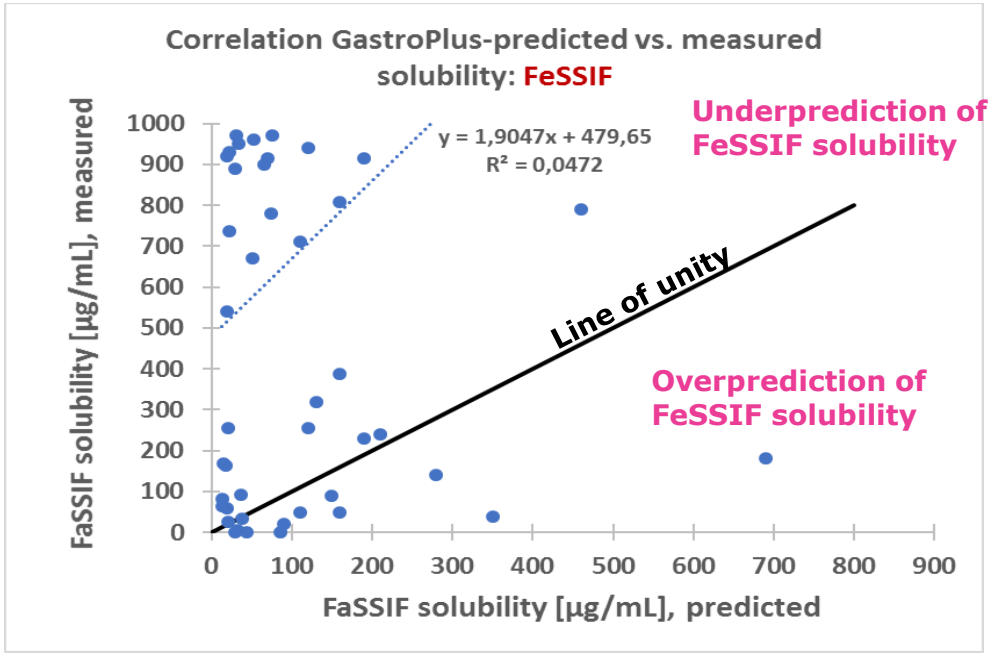
Case example 1: Predicted *vs.* observed solubility



Software-predicted* *vs.* measured FaSSIF/FeSSIF solubility

- 46 EMD compounds (LO thru Ph3)
- Mainly weak bases

* GastroPlus 9.5



	FaSSIF	FeSSIF
Within 2-fold	33%	9%
Within 5-fold	24%	26%
Outside 5-fold	43%	65%

→ Poor correlation between predicted and measured biorelevant solubility

Conclusion

Software tends to underpredict actual FaSSIF/FeSSIF solubility

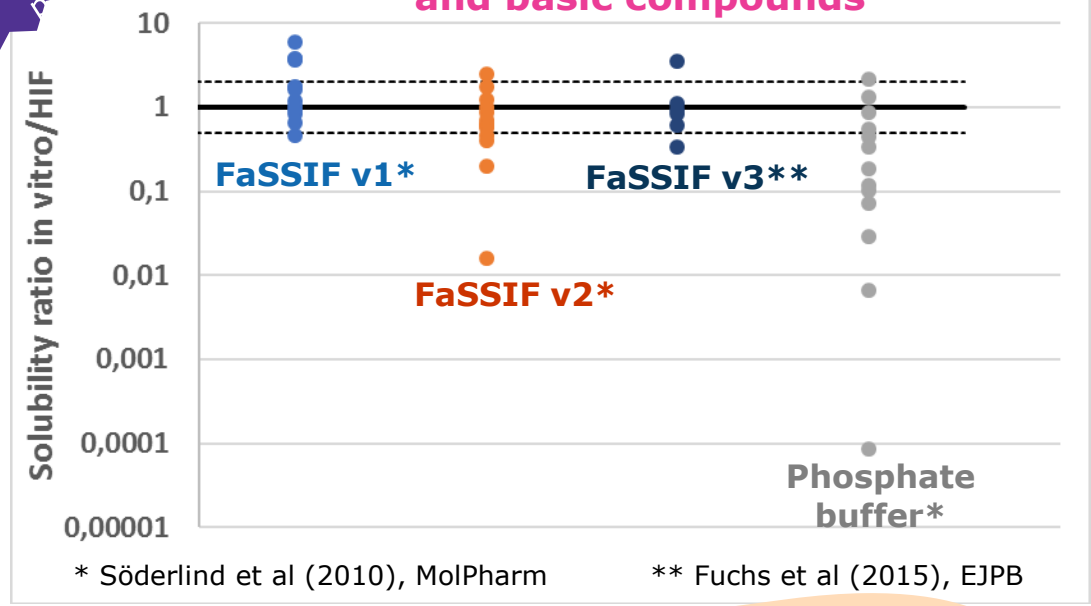
Use measured solubility as early as possible

Best practice: Solubility

Case example 2: Predictive performance of FaSSIF versions

Not ionized at neutral pH

Solubility ratio (*in vitro*/HIF) of neutral and basic compounds



* Söderlind et al (2010), MolPharm ** Fuchs et al (2015), EJPB

Number of cases

	FaSSIF v1	FaSSIF v2	FaSSIF v3	Phosphate
N_{total}	13	13	6	13
N_{basic}	5	5	2	5
$N_{neutral}$	8	8	4	8

***In vitro* within 2-fold of observed**

	FaSSIF v1	FaSSIF v2	FaSSIF v3	Phosphate
N_{total}	8/13 (62%)	7/13 (54%)	4/6 (66%)	3/13 (23%)
N_{basic}	3/5 (60%)	1/5 (20%)	1/2 (50%)!	0/5 (0%)
$N_{neutral}$	5/8 (63%)	6/8 (75%)	3/4 (75%)!	3/8 (38%)

FaSSIF v1: Slight trend for over-prediction

FaSSIF v2: Slight trend for under-prediction

FaSSIF v3: Seems ok (but many outliers of FaSSIF v1 and v2 not included in FaSSIF v3 analysis)

Phosphate: Pronounced under-prediction

Conclusion

Based on literature data, FaSSIF v1 seems to be most predictive for *in vivo* solubility in HIF. For FaSSIF v3, the basis of data is even smaller.

Best practice: Solubility

Case example 3: "Literature says"*

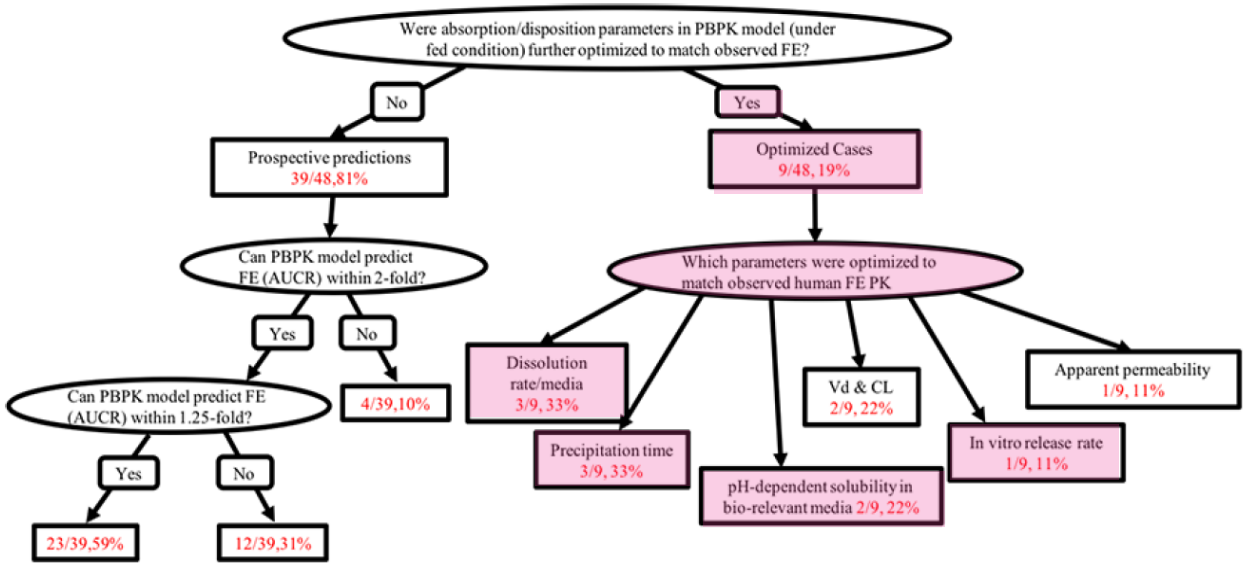
REVIEW

Predictive Performance of Physiologically Based Pharmacokinetic Models for the Effect of Food on Oral Drug Absorption: Current Status

Mengyao Li[1,2*], Ping Zhao[1,3], Yuzhuo Pan[4] and Christian Wagner[1,5]

CPT Pharmacometrics Syst. Pharmacol. (2017) **00**, 00; doi:10.1002/psp4.12260; published online on 0 Month 2017.

- 15 peer-reviewed publications and 2 FDA reviews
- 27 compounds (22 basic; 2 acidic; 2 ampholytes; 1 neutral) with 48 food effect simulations
- 63% poorly soluble, 15% highly soluble, 22% n.a.
- Fa < 50% in approximately 50% of cases
- 81%: Prospective simulations; 19% optimized fed parameters



- Fitted parameters if fed simulation did not fit to observed data: Dissolution/release rate, precipitation parameters, solubility.
- "Input parameters for both absorption and disposition models could be obtained from various sources, reflecting a lack of standardization and large variability in the quality of input data."
- Physiology not always reflected well in PBPK software tools, leading to mis-prediction of site-specific solubility (fed gastric physiology; dynamic decrease of pH over time in fed stomach; liquid volumes in colon)

Conclusion

Evidence for dis-connect between *in vitro* and *in vivo* solubility. Physiology in PBPK tools needs improvement.

* Li et al (2017), CPT-PSP

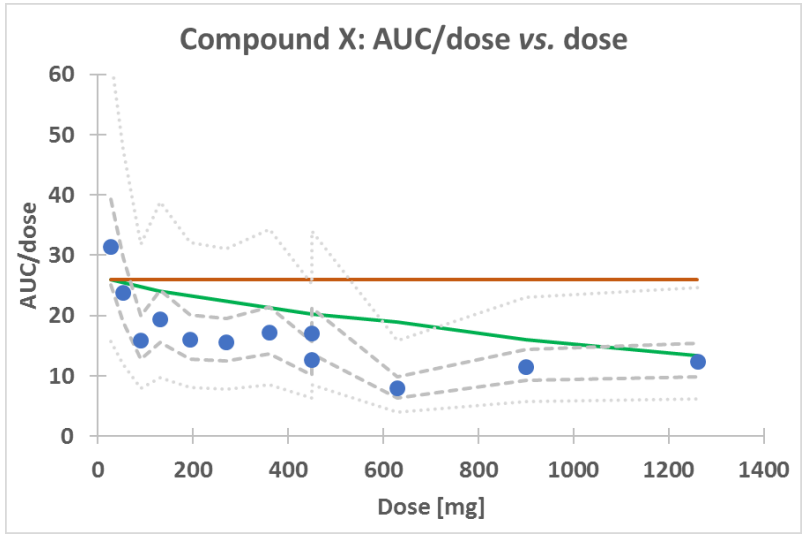
Best practice: Solubility
Case example 4: Ion-effect

EMD compound X shows ion-effect, with significantly impaired solubility in the presence of physiological chloride concentration.

pH	Solubility of compound A [mg/mL]	
	Without Cl-	With 100 mM Cl-
1.1	~ 1	~ 0.01
4.5	~ 0.7	~ 0.007
6.8	~ 0.04	~ 0.004

Use PBBM to 1) set specs for PSD and 2) de-risk BE study. But: Which solubility input to use?

What is the impact on simulations…



… and decision-making?

BCS class 4

- **Ion effect considered:** BE correctly predicted, formulation development de-risking successful
- **Ion effect not considered:** Overprediction of absorption, successful BE prediction jeopardized

Conclusion

Test if compound shows ion effect. If so: Take effect into account, especially if the compound is poorly soluble.

Experience for comparably **highly soluble compounds** (BCS 1; DCS 1/2a): **No pronounced impact** if ion effect is reflected in solubility input (D/S ratio reasonably low even in presence of counter ions).

Best practice: Solubility

Case example 5: Impact of puffer species on solubility of pazopanib

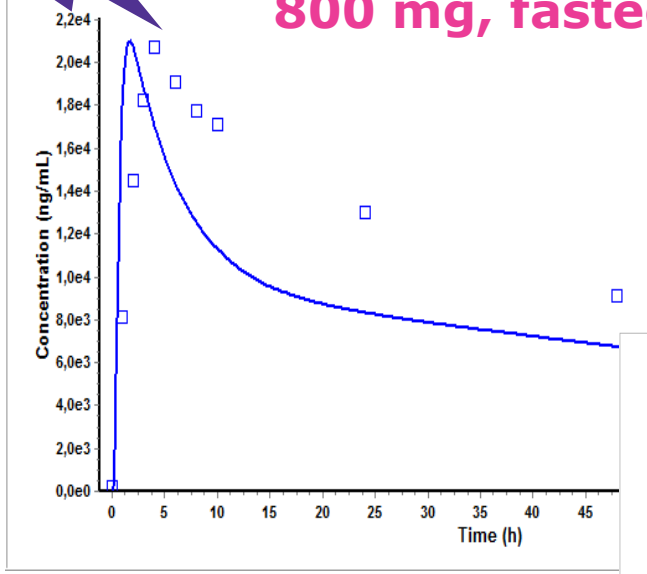
IQ Consortium

Pazopanib	
pKa	~ 2 (b); ~ 6 (b)
Solubility [µg/mL]	~ 1 (FaSSIF), ~ 3 (FeSSIF)
Permeability	High (Caco2)
Question	FIH: Absorption limitations?
BA (fasted)	~ 25%
Absorption	Dose-dependent; impaired (fasted)
Food effect	~ 2-fold @ 800 mg
Question	Predict food effect

Modeling strategy

- Absorption model: Measured solubility; Caco2 permeability. Fit precipitation time to match PK from SAD.
- Post-absorptive DD: From IV data

800 mg, fasted



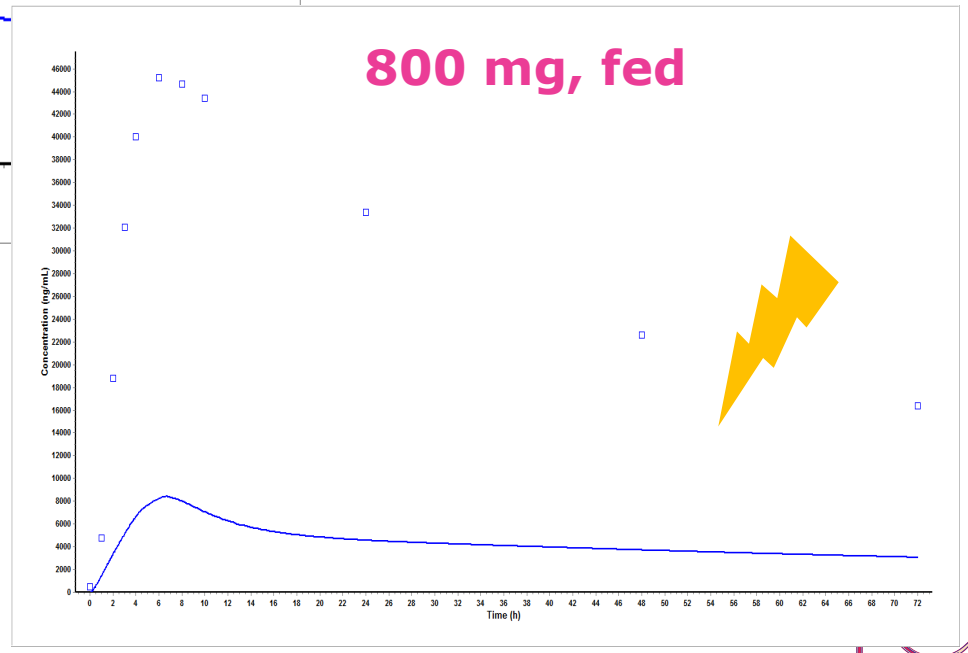
Fasted

- AUC, Cmax, tmax within 2-fold of observed data
- Shape ☹
- Successful verification?

Fed

- Negative food effect predicted (low solubility; shortcomings software)
- Predictivity of FaSSIF/FeSSIF solubility for pazopanib?

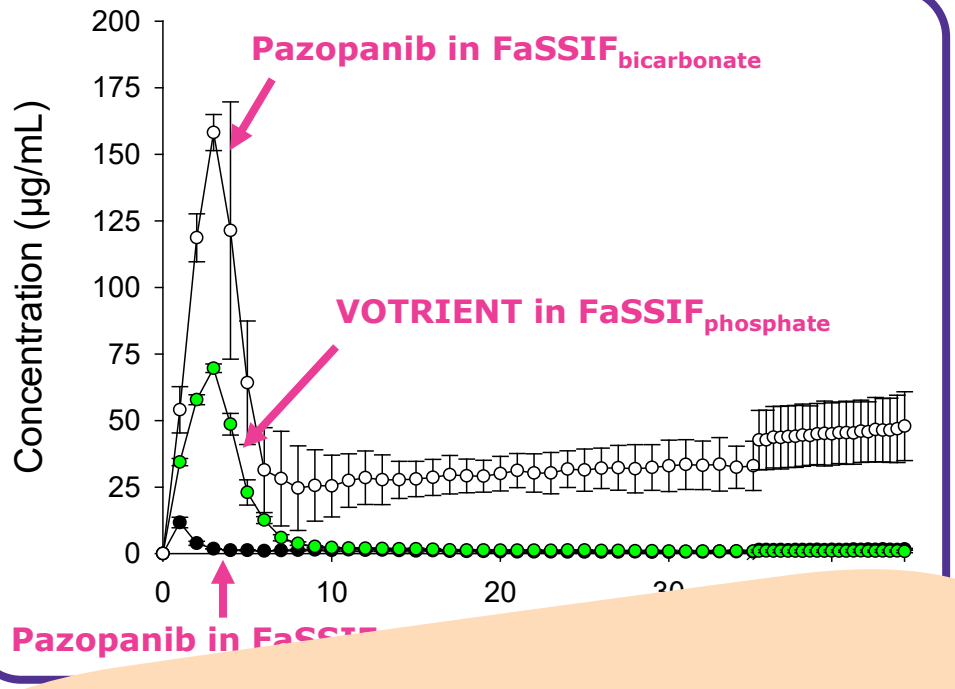
800 mg, fed



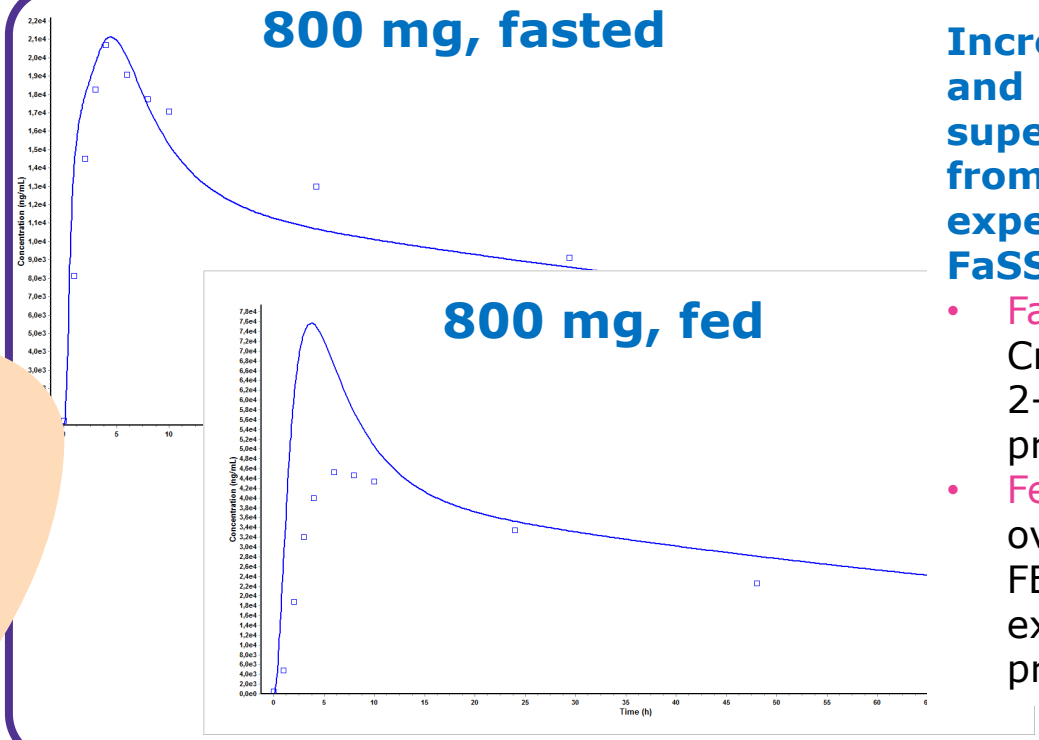
Best practice: Solubility

Case example 5: Impact of puffer species on solubility of pazopanib

Transfer model and the use of a more biorelevant bicarbonate buffer*,**



- Physiological buffer species in gut: Bicarbonate, not phosphate**
- Very pronounced increase in solubility and supersaturation when going from FaSSIF$_{phosphate}$ to FaSSIF$_{bicarbonate}$.



Increased solubility and supersaturation from transfer experiments in FaSSIF$_{bicarbonate}$

- Fasted: AUC, Cmax, tmax within 2-fold, acceptable profile shape
- Fed: Slight overestimation of FE, but trend and extent of FE were predicted well.

Conclusion

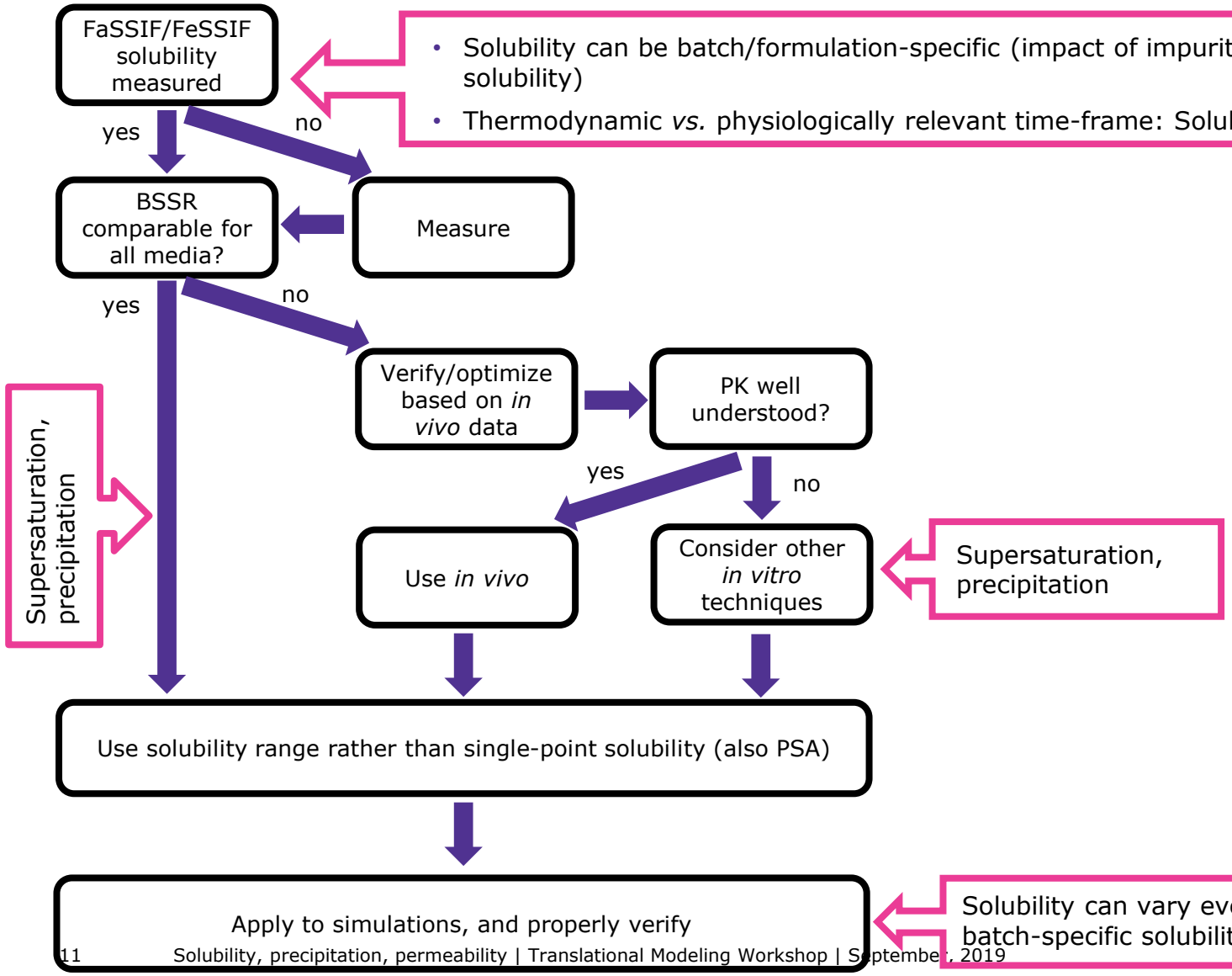
For challenging compounds, a more biopredictive solubility medium / setup may yield better simulation results

…g., McConnell et al (2008) IntJPharm]

** Jede et al (2019) MolPharm

Best practice: Solubility

Summary



- Solubility can be batch/formulation-specific (impact of impurities, polymorphs, solid state excipients on API solubility)
- Thermodynamic *vs.* physiologically relevant time-frame: Solubility kinetics

Common ion effect?

Surface pH: See Xavier's presentation

Solubility can vary even between clinical (GMP) batches – measure batch-specific solubility and apply to simulations

02

Supersaturation and Precipitation

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Best practice: Supersaturation and precipitation
Methods to predict precipitation

See Ed's presentation for more details

In vitro assays

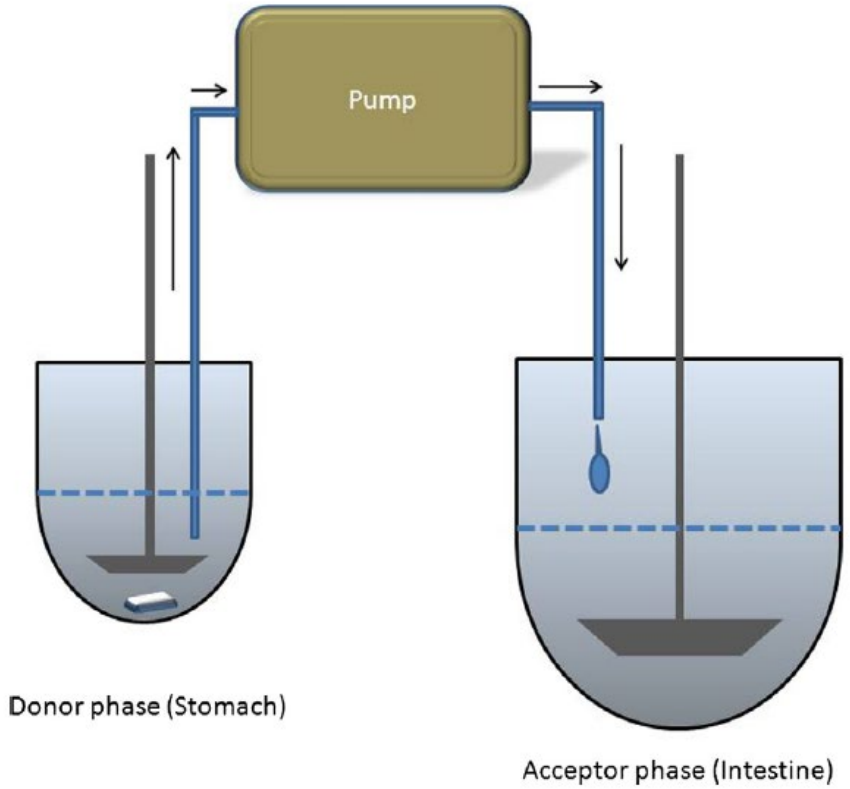
- Dumping experiments [Kambayashi et al (2016) EJPB; Jakubiak et al (2015) MolPharm]
- Two-compartmental transfer model [Kostewicz et al (2004), JPharmPharmacol)] and variations thereof [e.g., Jede et al (2018), JPharmPharmacol]
- Multi-compartmental models, also accounting for drug absorption [e.g., Gu et al (2005), JPharmSci; Psachoulias et al (2012) PharmRes; Kourentas et al (2016) EJPharmSci]
- Bi-phasic precipitation experiments [e.g., Tsume et al (2018) JPharmSci]
- TNO model (TIM-1, TIM-2)

In silico approaches

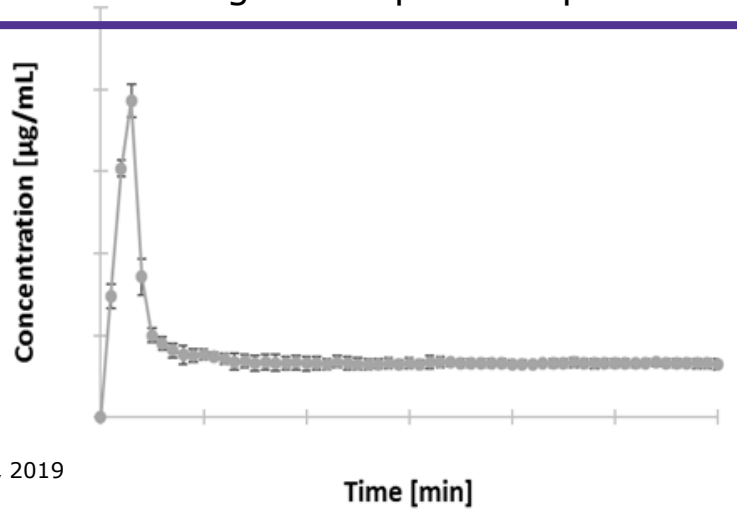
- Approaches based on classical nucleation and crystal growth theory [e.g., Carlert et al (2010) PharmRes]

Best practice: Supersaturation and precipitation

Reminder: Transfer model



- Example for precipitation setup which does not take absorption into account
- Two-compartmental model, based on USP 2 apparatus [Kostewicz et al (2004), JPharPharmacol], or mini-scale [Jede et al (2018), JPharPharmacol] for preformulation application
- Simulated stomach (donor), containing SGF (or versions thereof)
- Simulated intestine (acceptor), containing FaSSIF (or versions thereof)
- Transfer of API solution/suspension from "stomach" to "small intestine" via pump, and measurement of concentration of dissolved drug in acceptor compartment



Best practice: Supersaturation and precipitation

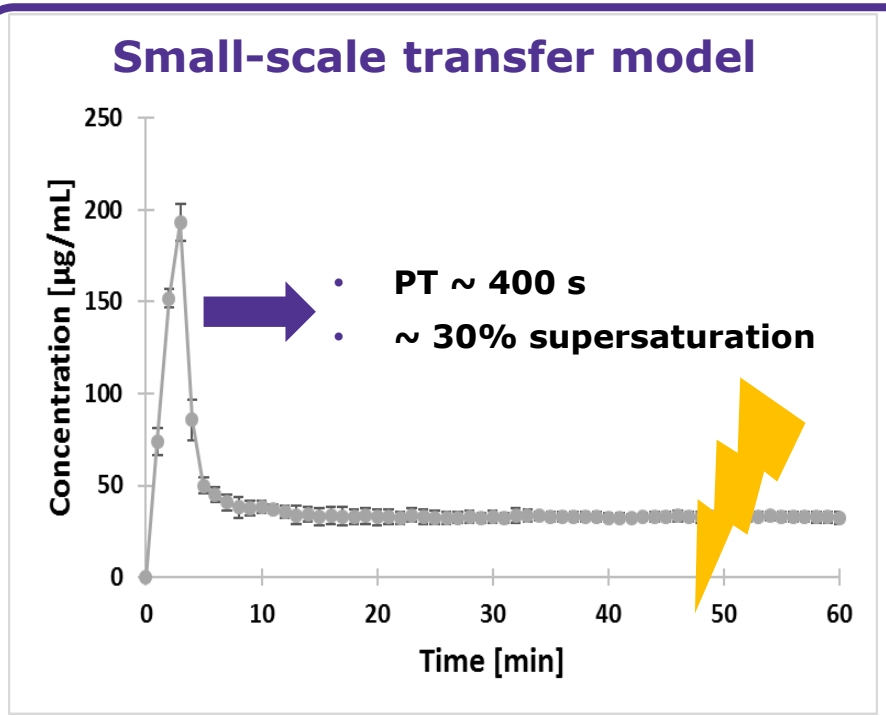
Case example 1: Transfer model to simulate precipitation of Cpd A

Compound "A", EMD Serono	
pKa	~ 6 (b)
Solubility [µg/mL]	~ 30 (FaSSIF)
Permeability	High
Question	FIH: Absorption limitations?

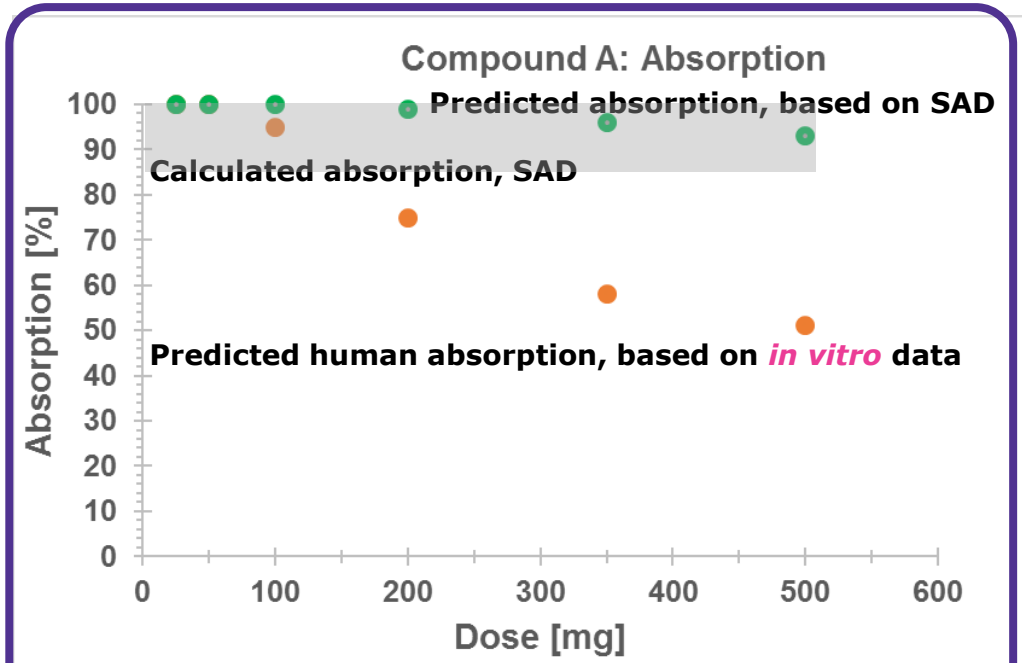
Scaling of precipitation parameters from *in vitro* data

- Transfer model: Pronounced underprediction of absorption at medium/high doses, assay not predictive (lack of absorption sink)

Small-scale transfer model



PBBM



Best practice: Supersaturation and precipitation

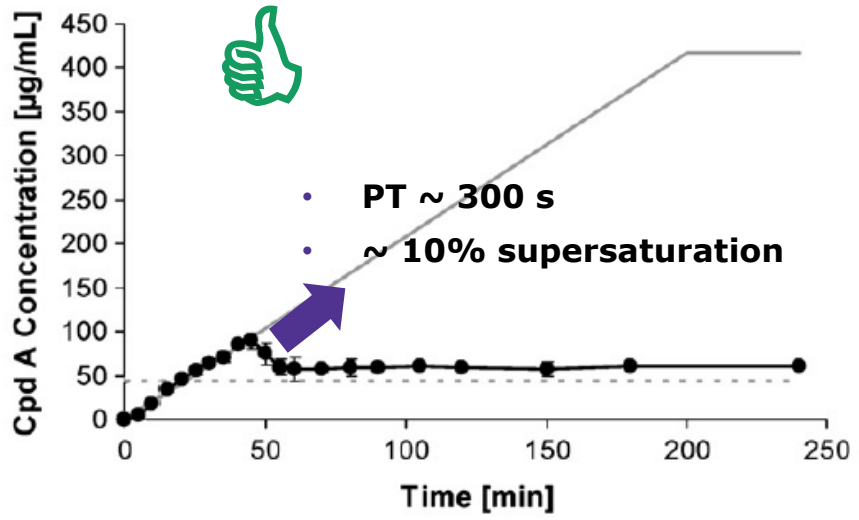
Case example 2: Transfer model to simulate precipitation of Cpd B

Compound "B", Merck & Co	
pKa	~ 4 (b); ~ 8 (b)
Solubility [µg/mL]	~ 50 (FaSSIF)
Permeability	Low (BCS 4)
Question	Precipitation impacts absorption?

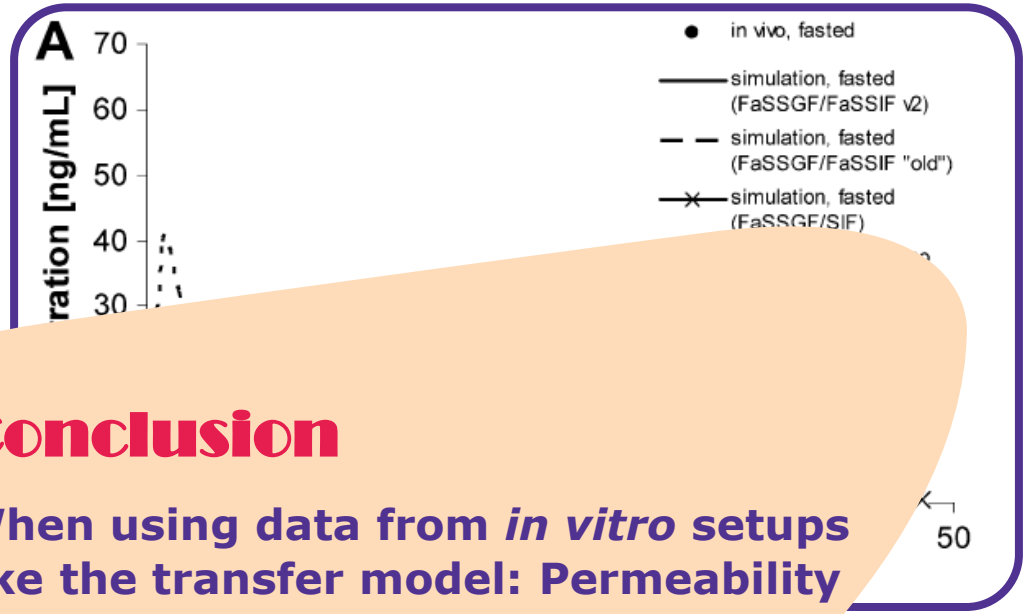
Wagner et al (2012), EJPB

Scaling of precipitation parameters from *in vitro* data

- Transfer model: Good prediction of Compound B PK profile using *in vitro* precipitation data as input parameter for the model
- Lack of absorption sink not deemed critical, as compound yields low permeability anyway



PBBM



Conclusion

When using data from *in vitro* setups like the transfer model: Permeability matters…

Best practice: Supersaturation and precipitation

Case example 3: FIH absorption prediction, optimization based on animal PK

Compound "C", EMD Serono	
pKa	~ 5 (b)
Solubility [µg/mL]	~ 3 (FaSSIF); < LOQ @ pH > 4 → ASD
Permeability	High
Question	Predict FIH absorption

Initial approach

- Build bottom-up model, using measured pH-dependent and biorelevant solubility
- Dumpin

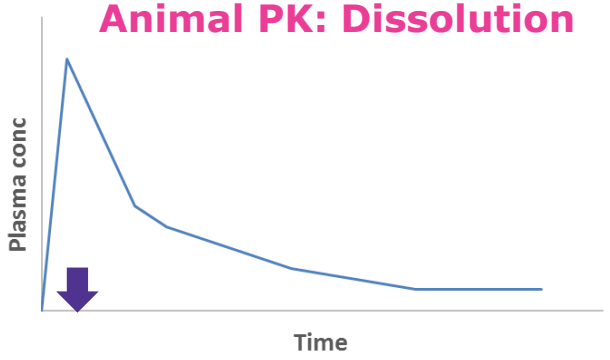
Conclusion

Good extrapolation from animal PK to human, also for many other compounds. Cave: Species differences

Complex formulation, high uncertainty

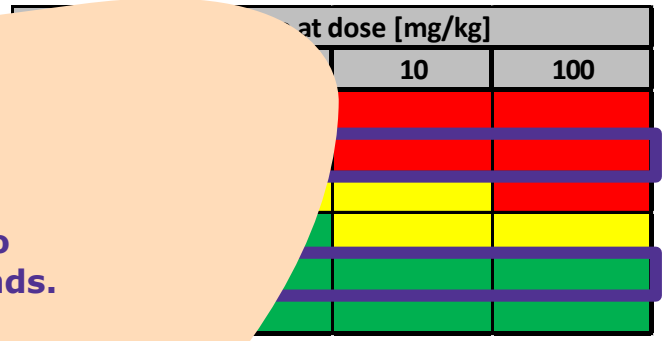
Simulate range rather than single value

Animal PK: Dissolution



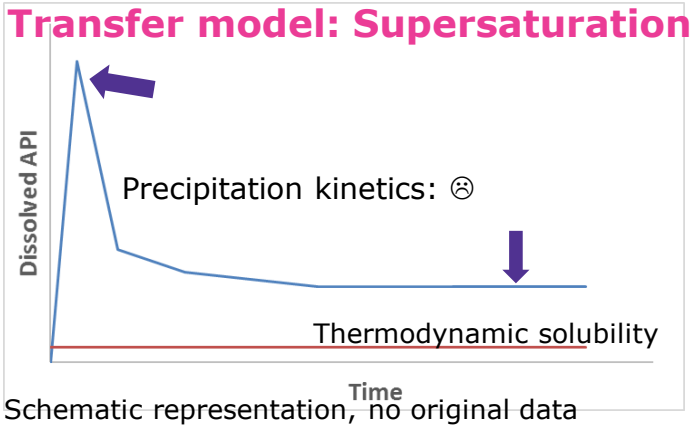
Schematic representation, no original data

Early tmax across species and dose levels: Fast dissolution from ASD, precipitation to govern fraction dissolved.



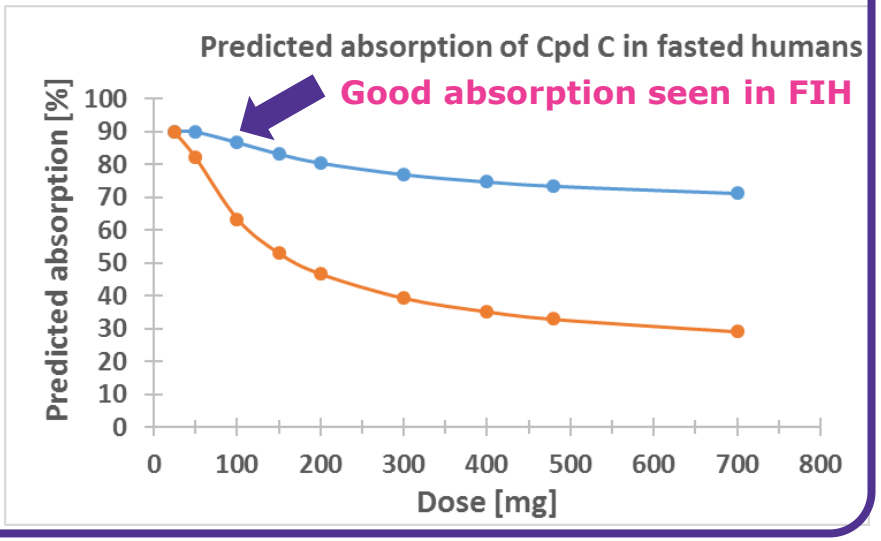
cipitation time which fits
ved exposure (AUC, Cmax,
r each species and dose level
nple: Rats)

Transfer model: Supersaturation



Schematic representation, no original data

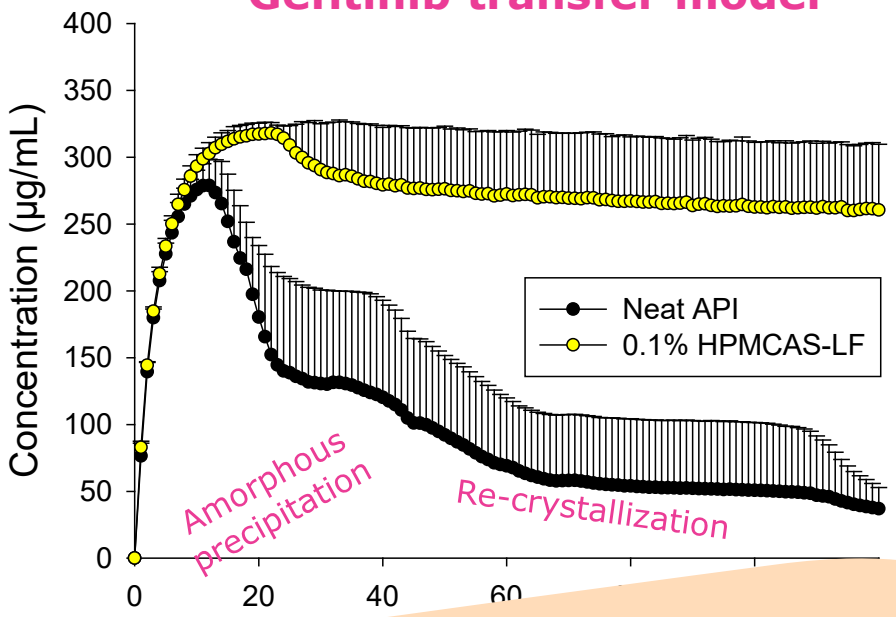
Which value to use? Peak concentration or stable supersaturation? Conservative estimate used.

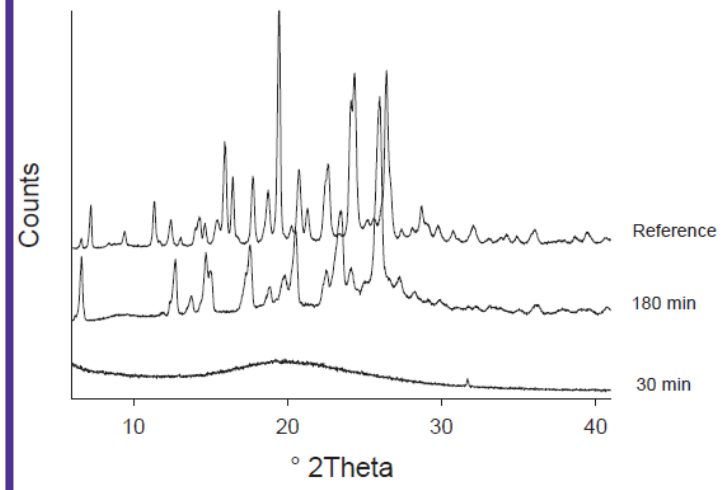


Best practice: Supersaturation and precipitation

Case example 4: Precipitate ≠ precipitate

Gefitinib transfer model





- Multi-phasic precipitation
- Amorphous precipitate confirmed after 30 min (intermediate supersaturated state)
- Slow re-crystallization

Conclusion

Precipitate ≠ precipitate. Characterization of precipitates, incl. re-dissolution, is thought to improve predictive performance for challenging compounds.

Presence of amorphous precipitates confirmed using transfer model

Gefitinib shows very high PK variability. Reasons not yet clear (genetic CYP polymorphism; gastric emptying; precipitation?)

- Though no PBBM was conducted for gefitinib, relevance of *in vitro* results for absorption modeling is deemed to be high (supersaturation; decreased precipitation)
- Only very few cases where amorphous precipitation of weak bases has been described in the literature. Future investigations needed.

Best practice: Supersaturation and precipitation
Summary

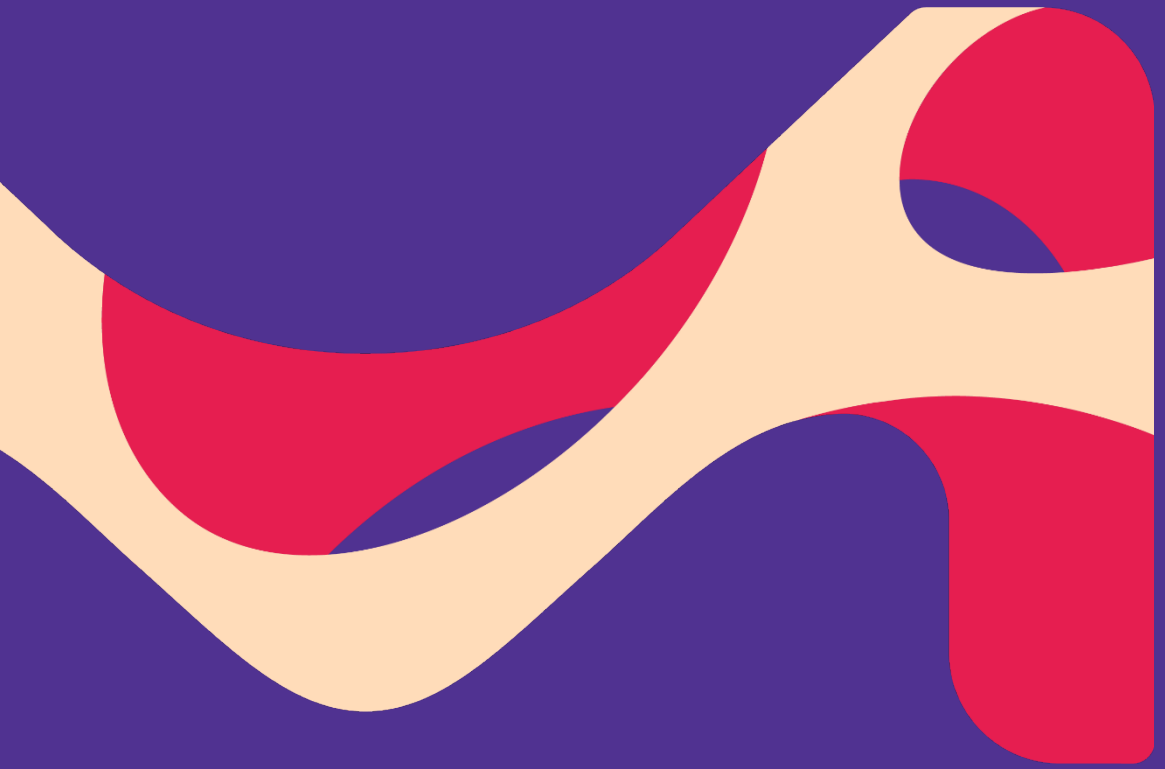
- **Some approaches reported in literature, most of them describing good predictivity of the assay.**
- **No systematic evaluation available.**
- **Internal experience with *in vitro* setups to predict precipitation: Mixed. Publication bias?**

Supersaturation: *In vivo* solubility often higher than what is measured *in vitro*. Supersaturation observed in *in vitro* setups seems to be a more predictive value than (thermodynamic) solubility.

Best practice?

Precipitation kinetics: Limited confidence in predictive performance of *in vitro* precipitation models

Optimizing precipitation parameters based on *in vivo* data currently seems to be the approach with the highest confidence.



03

Permeability

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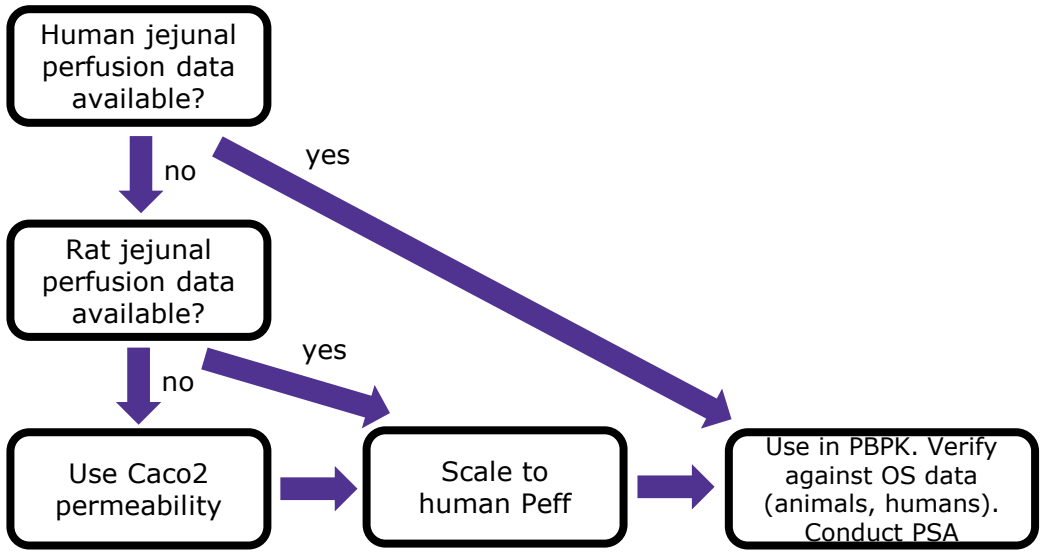
Best practice: Permeability
Passive, transcellular absorption

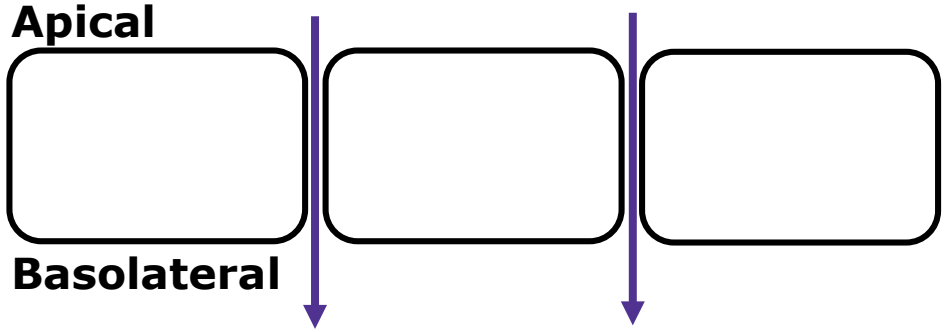
- Presumably most accurate estimate for permeability: (Rat) jejunal perfusion, which is also accepted for BCS classification [e.g. Kesisoglou (2013) AAPSJ]
- Caco2 assay (other cells; PAMPA) standard assay in industry. Important: Scaling from *in vitro* data to *in vivo* situation, using set of calibrants → Peff



Open questions, current gaps	
Level of "accuracy"	How much do we need when permeability is high anyway?
Optimization of permeability	How to optimize when no OS available / dissolution is assumed to decelerate absorption?
Food/excipients	How to model?
Drift of particles into UWL	Is permeability a function of dose? [Sugano (2013) IntJPharm]
Saturable active transport	Low basis of data. Lack of experience. Scaling from in vitro to in vivo.
Colonic absorption	Overestimated? [Kesisoglou (2013) AAPSJ]

Best practice: Permeability

Paracellular absorption



Paracellular absorption: Considered to contribute only marginally to overall absorption

- Often small, hydrophilic molecules
- Very few reports describing how paracellular absorption is handled in PBPK, thus limited experience
- Rule of thumb [Peters (2008)

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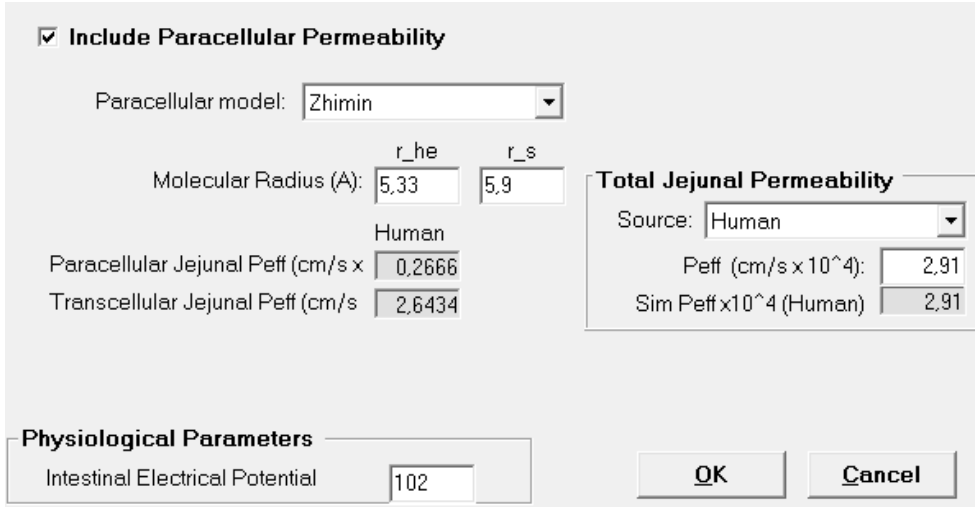
Conclusion

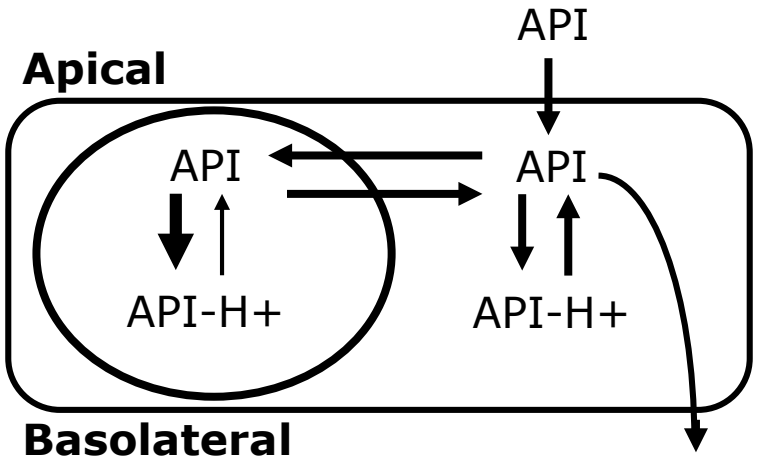
- **More experience needed**
- **"Best practice": ?**



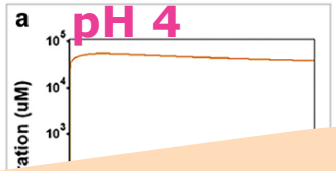
Example: GastroPlus 9.7

- If compound is assumed to have paracellular absorption: Use build-in calculator (input needed: Calculated Peff; molecular radius)
- Internal experience: Paracellular absorption usually not taken into account.

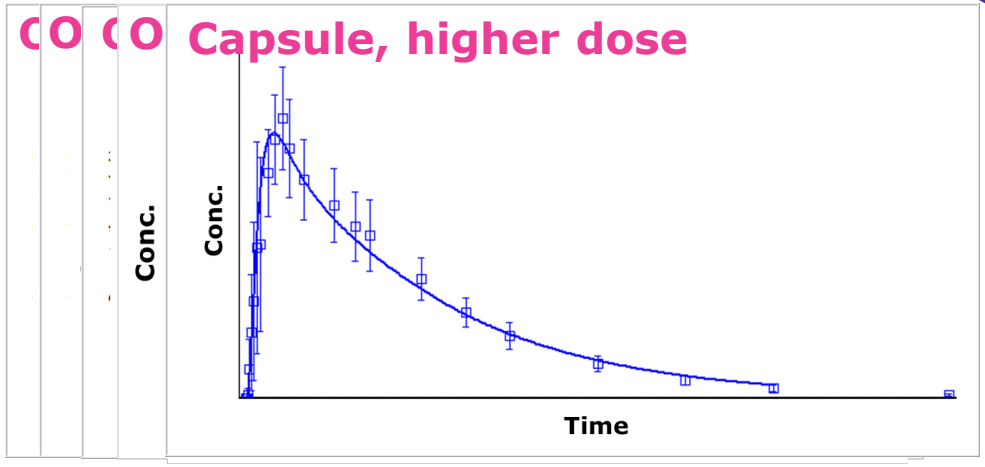
Best practice: Permeability
Lysosomal trapping



- Trapping of lipophilic, ionizable compounds described for several compounds (antipsychotics; TCA; SSRI; dextromethorphane, amodiaqui



- EMD compound C: Lipophilic base
- Late tmax values (6 – 10 h), independent from formulation (OS, capsule, tablet)
- Model building to set dissolution specifications for BE study



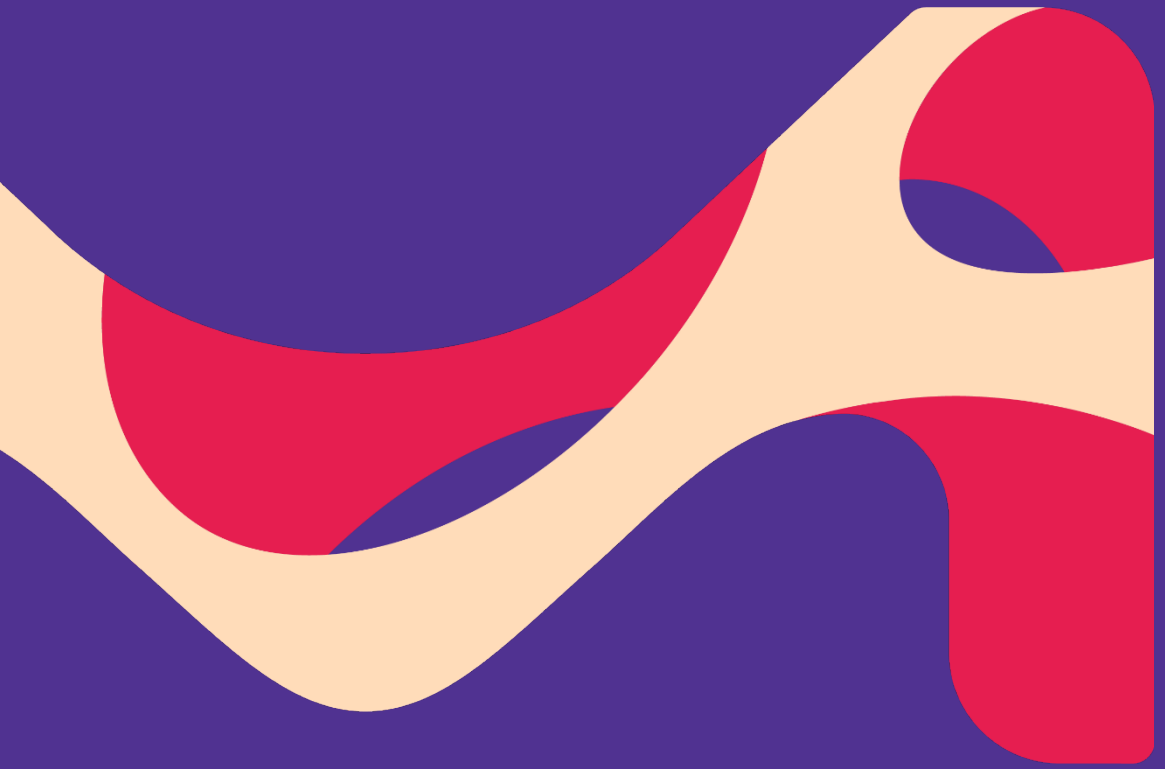
ations:

- solution: Cmax/tmax not captured well
- mizing permeability did not yield good results (tmax too early or absorption low)
- ld lysosomal trapping into the model: Decrease fu,ent from 100% (default) to % (fitted) to slow down mass transfer from enterocytes into systemic circulation [Bolger et al (2019), JPharmSci].
- Good fit of data for oral solution. Model was subsequently used successfully to simulate PK for various oral formulations, incl. BE study.

Conclusion

- **Differentiation low permeability *vs.* trapping**
- **Semi-mechanistic simulation of lysosomal trapping seems feasible**

1 Daniel (20 ispos; 3 Nadanavic et al (2011), Toxicol in vitro; 4 De Duve et al (1974) BiochemPharmacol



04

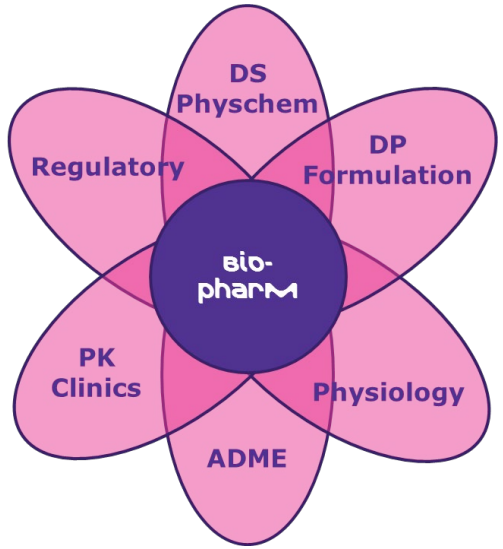
Conclusion

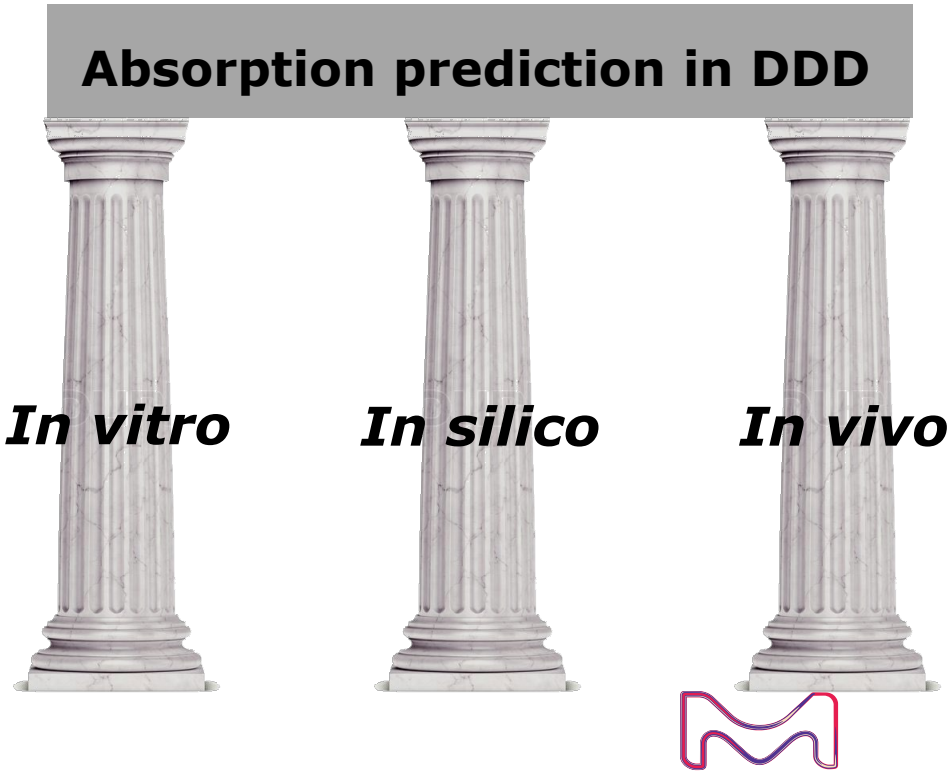
EMD SERONO

Building absorption models with high confidence:

We are on a good way, but we are not yet there – especially for drugs with low to moderate absorption

- What is the most predictive biorelevant medium?
- Scaling of precipitation from *in vitro* to *in vivo*
- Permeability aspects, esp. active transport
- Shortcomings in current PBPK software





Thank you for your attention ☺

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