Optimal Use of Static and Dynamic Models for DDI Assessment along the Value Chain

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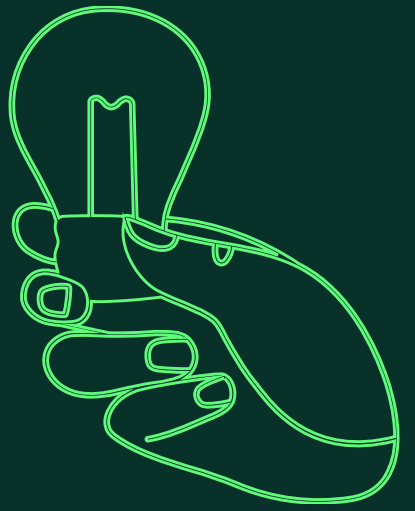

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Executive Summary

BACKGROUND INFORMATION

1

Quantitative predictions with MSM?

ICHM12: possible with more relevant precipitant concentrations

Literature: possible with unbound organ exit precipitant concentration for CYP-mediated reversible inhibition, TDI and induction as well as transporter-mediated (OAT3) DDI

2

Rationale for quantitative predictions from MSM, comparable with PBPK

Prediction accuracy of both static and dynamic models is limited by same factors

Dynamically varying [I] is not necessary for estimating AUCR, a non-dynamic measure of DDI risk

PROPOSALS

3

When simplicity can serve the purpose

When parameter non-identifiability cannot be resolved through data generation in clinic, MSM predictions under worst case scenario may serve as an alternative

4

Optimal use of predictive models

Leverage strengths of MSM (fast, minimal assumptions) and PBPK (Cmax estimation, population extrapolation) for an intended use

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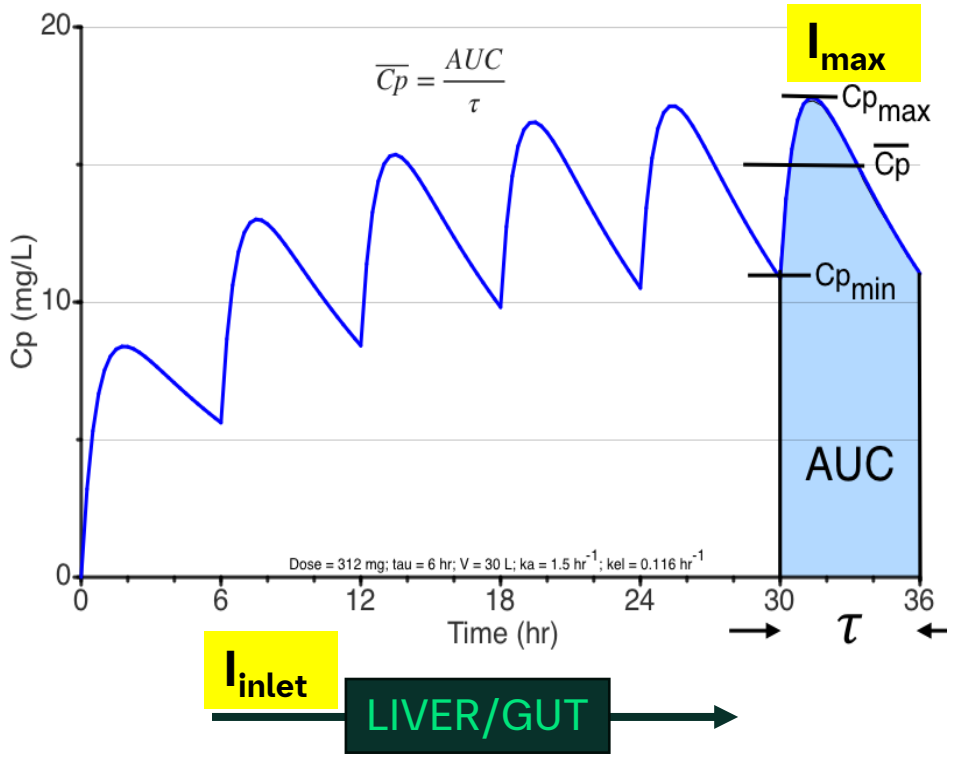
MSM equations - Back-up

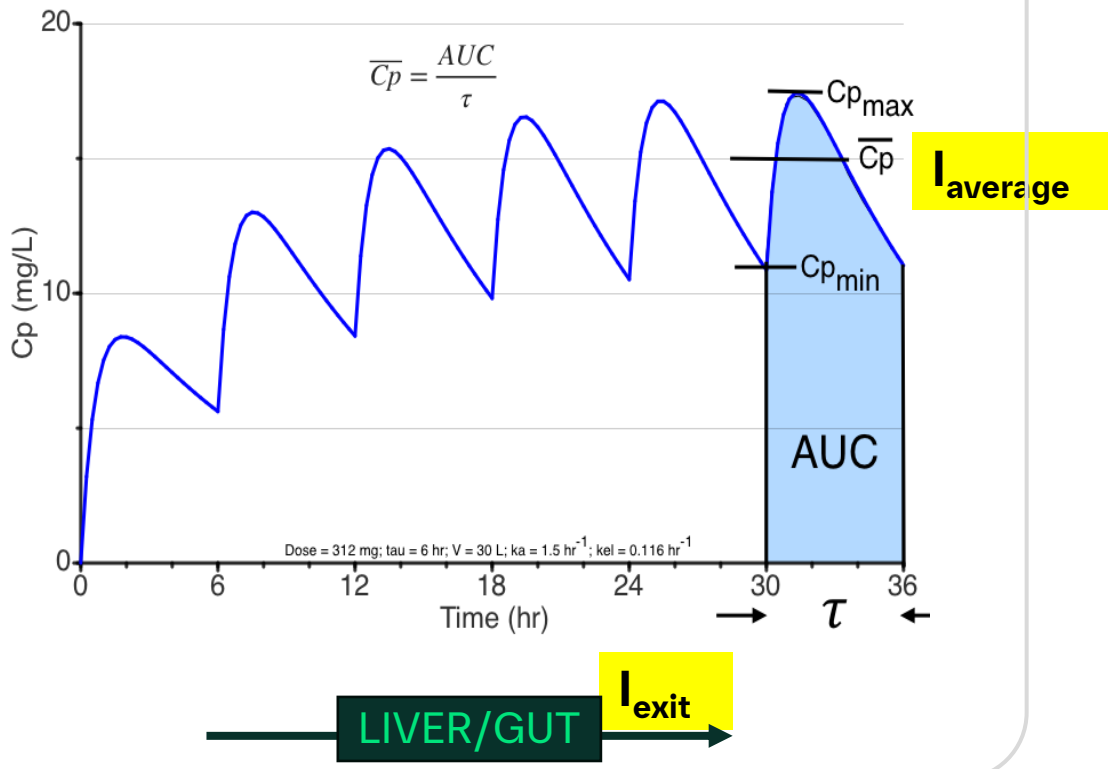
Quantitative predictions with MSM possible with average organ exit [I]

- Traditionally, basic and mechanistic static models (MSM) have been used for screening rather than for quantitative predictions of DDI.
- ICH M12 acknowledges the application of MSM for quantitative predictions when appropriate driver precipitant concentrations in gut and liver are used.

MSM (Screening): ICH M12



MSM (Quantitative)



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Equations -Back-up

Enzyme-mediated DDI

[I]g, [I]h for screening and quantitative prediction applications with MSM

Precipitant concentrations recommended in MSM in ICHM12 overestimate DDI risk and are useful for screening
Use of **average, organ exit precipitant concentration** in MSM show quantitative predictions, comparable with PBPK

$$[I]g = Fa \times ka \times Dose / Qen$$

$$[I]h = [I]_{max,inlet,u} = fu,p \times (C_{max} + (Fa \times Fg \times ka \times Dose)/Qh/RB)$$

Screening, ICH M12
Requires ka

$$[I]g = C_{avg,portal,u} = fu,p \times (C_{avg} + (Fa \times Fg \times Dose)/\tau/Qpv/RB)$$

$$[I]h = C_{avg,systemic,u} = fu,p \times C_{avg}$$

Organ exit precipitant concentration
Quantitative predictions
No ka

FaFg cannot be estimated without IV PK. The assumption FaFg = 1 is not valid for CYP3A substrates with high CL.

fu,p	Unbound fraction in plasma. Sensitivity analysis for fu,p is needed for highly protein bound drugs.
C_{max}	Maximal total inhibitor concentration observed in plasma at steady state.
C_{avg}	Average total inhibitor concentration observed in plasma at steady state.
Fa	Fraction absorbed after oral administration; a value of 1 (worst-case) used when data is not available.
Fg	Fraction available after intestinal metabolism; a value of 1 (worst case) used when data is not available.
ka	First order absorption rate constant in vivo; a value of 0.1 min^{-1} (worst case) used when the data is not available.
τ	Dosing interval
RB	Blood-to-plasma concentration ratio.
Qen	Blood flow through enterocytes (e.g., 18 L/h/70 kg).
Qh	Hepatic blood flow (e.g., 97 L/h/70 kg).
Qpv	Hepatic portal vein blood flow, which is ~75% of hepatic blood flow = 72.8 L/h/70 kg

Details - Back-up

Enzyme-mediated DDI

Comparison of PBPK and MSM (not exhaustive)

Quantitative predictions, comparable with PBPK demonstrated with average organ exit concentrations (C_{avg} (hepatic) and $C_{avg,portal}$ (gut))

Type of DDI	Number of Interactions	[I]	Reference
CYP3A TDI	59	Hepatic $C_{max,inlet}$	HJ Einolf, Xenobiotica (2007)
CYP3A TDI	54	C_{avg}	Y-H Wang, DMD (2010)
CYP3A **Reversible**	35	C_{avg}	EJ Guest, BJCP (2011)
CYP3A (16) **CYP2D6** (3) reversible and TDI	19	Compared hepatic $C_{max,inlet}$ & C_{avg}. Better results with C_{avg}	SA Peters, DMD (2012)
CYP3A **TDI**	23	Avg organ exit concentrations	E Tseng DMD 2021
CYP3A (31), **CYP2C9** (39), **CYP2C8** (15) reversible	90	C_{avg}	JD Gomez-Mantilla et al, Clin PK (2023)

Best predictions with average organ exit concentrations

CYP3A **induction**	51	Avg organ exit concentrations	Ramsden and Fullenwider EJDMPK(2022)

Details - Back-up

Transporter-mediated DDI

Precipitant concentrations for screening and quantitative predictions

Type of DDI	Screening (Draft ICH M12)	Quantitative predictions	Quantitative predictions -Comments | Reference
Intestinal **(P-gp, BCRP)**	[I]g	$C_{avg,portal\ vein}$ (?)	Large inter-lab variability in Ki reported for P-gp.
Hepatic uptake **(OATP1B)**	[I]h	*Liver: [I]h = $C_{max,inlet}$	MSM and PBPK comparison for investigational drug as precipitant Sane et al, DMD (2020)
Renal uptake **(OAT1/3)**	C_{max}	Observed C_{avg}	MSM and PBPK comparison for investigational drug as substrate Gomez-Mantilla et al, Clin PK (2023)
Renal uptake & efflux **(OCT2, MATE)**			Different in vitro assay designs, including substrate and cell systems used, strongly influence the IC_{50} derived and contribute to high variability across laboratories Krishnan et al, CPT (2022)

*Resulted in over-prediction. More realistic estimates may be possible with [I]h = $C_{avg,portal\ vein}$

Predictive models for DDI assessments

Mechanistic Static Models (MSM) for comparison with PBPK

Use same input data in both models. **Parameter optimisation** with MSM using the same workflow as for PBPK

Predict DDI with available data

- **Precipitant:** average concentration (clinical PK);
- in vitro interaction parameters, protein binding data: same as used in PBPK
- **Object:** phenotyping (or mass balance data): same as used in PBPK; CL (clinical data); Fgut =0.5
- Sensitivity analysis to cover for uncertainty in in vitro data used as input

Confirm prediction with clinical DDI

- **Adopt the same work-flow as in PBPK**, for confirming interaction parameters (precipitant) or phenotyping data (object of DDI) for investigational drug with clinical PK and DDI: derive fm,CYP, fT from observed clinical PK. Adjust the parameters for investigational drug in MSM, until the model-predicted AUC ratio matches the observed ratio.

Predict untested scenario

- **Investigational drug as precipitant:** Predict DDI at doses not tested in the clinic
- **Investigational drug as object of DDI:** Predict DDI for co-administration with moderate precipitants; predict effect of modulators on PM &UM populations using clinical DDI on EM & IM;
- Effect of modulators on SS exposure of substrates with time-varying clearance using clinical DDI study with single dose of substrate.

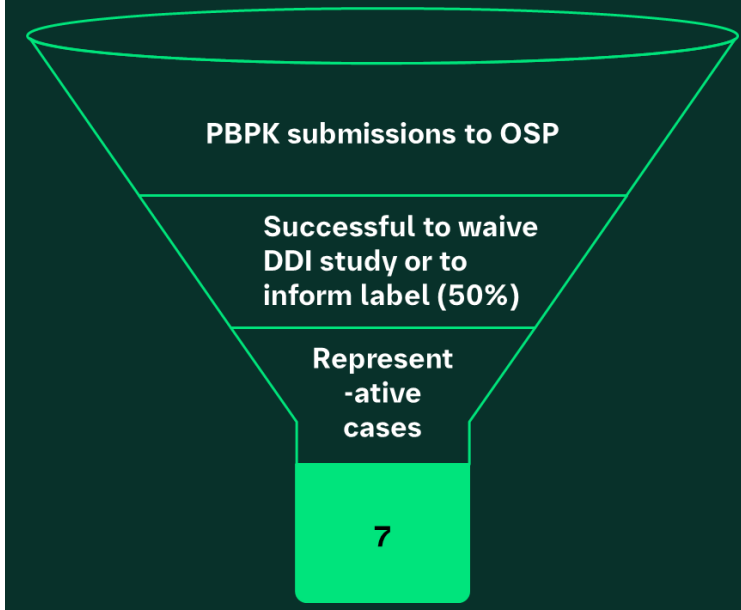
Can Mechanistic Static Models for Drug-Drug Interactions Support Regulatory Filing for Study Waivers and Label Recommendations?

Gomez-Mantilla et al, Clinical Pharmacokinetics 2023

Investigational drug*	Prediction	Label	Comments
Voxelotor (CYP3A4)	Different registrational dose to one in DDI study	Contraindication of sensitive substrates	Voxelotor has linear PK covering the 2 doses
Ivosidenib (inducer CYP3A4)	CYP3A induction on MDZ using autoinduction obsd in lieu of DDI study.	Contraindication of sensitive substrates	**Concurrent induction** with rifampin
Ibrutinib (CYP3A4)	Effect of moderate modulators using strong	Dose reduction with moderate inhibitors	**High CL,** sensitive substrate of CYP3A
Voxelotor (CYP3A4)	Effect of modulators	Dose adjustment with CYP3A modulators	Low CL: no gut DDI, multiple pathways
Siponimod (CYPs 3A4 & 2C9)	Effect of modulators on PM &UM populations using data on EM & IM	Contraindication of strong modulators, dual moderate in all; moderate inducer in PM	Low CL **Induction of both enzymes** by rifampin
Apalutamide (inducer & substrate of CYP3A, 2C8)	Effect of modulators on SS PK of apalutamide & its active metabolite using clinical DDI with single dose	No dose adjustment. No sig change in parent + active metabolite (NAPA) exposure	Low CL. **Concurrent induction** with rifampin.
Baricitinib (OAT3)	Effect of moderate inhibitors using strong	Mentions no dose adjust-ment for moderate inhibitors	Quantitative prediction -basal renal transporter

*Precipitant or object of DDI

No value addition of dynamically varying [I] for any of these applications



Hypothesis: the use of unbound average steady-state concentrations of modulators as driver concentrations in MSMs should lead to same conclusions as those from PBPK modelling for non-dynamic measures of DDI risk assessment (AUCR), if uncertainties in input data for the interacting drugs are resolved with clinical data in the same way

Can Mechanistic Static Models for Drug-Drug Interactions Support Regulatory Filing for Study Waivers and Label Recommendations?

Gomez-Mantilla et al, clinical Pharmacokinetics 2023

Compound	Mean MSM/PBPK prediction ratio	MSM/PBPK prediction ratios within the 0.8–1.25 interval
Voxelotor (inhibitor of CYP3A)	1.01	2 of 2
Ivosidenib (inducer of CYP3A)	0.95	0 of 2
Ibrutinib (substrate of CYP3A)	1.14	3 of 4
Voxelotor (substrate of CYP3A)	1.06	23 of 23
Siponimod (substrate of CYP3A and CYP2C9)	0.81	19 of 39
Apalutamide (substrate of CYP3A and CYP2C8)	1.00	9 of 15
Baricitinib (substrate of OAT3)	1.02	5 of 5

inducer and

1 MSM predictions of **concurrent induction** tend to be **more conservative** compared to PBPK

2 **Extensive gut contribution** to DDI. Use of $f_{u,gut}$ of 0.057 & altered CYP3A Ki for keto to simulate observed DDI in PBPK

3 MSM tends to be more conservative compared to PBPK in predicting DDI with rifampicin which induces both CYPs

4 MSM predictions of **concurrent induction** tend to be **more conservative** compared to PBPK

- None of the differences in predictions between methods were significant enough to have resulted in an altered regulatory decision
- **Ivosidenib, apalutamide, siponimod:** In the absence of clinical data, it is difficult to verify if MSM or PBPK predictions are better.
- IndC50 of rifampin was estimated from a clinical DDI study of oral rifampin 600 mg and iv midazolam 0.5 mg (1.9 uM)
- **Ibrutinib:** Differences only in CYP3 inhibition DDI, not induction. When gut contribution to DDI is high, it is difficult to estimate this due to **non-identifiability** in the absence of IV PK. Recent successful applications tend to be low CL drugs with low gut contribution

Prediction accuracy

Static and dynamic models differ in the way inhibitor concentrations are considered. How does this difference impact accuracy?

MSM: Rationale to consider Cavg for reversible, TDI, induction

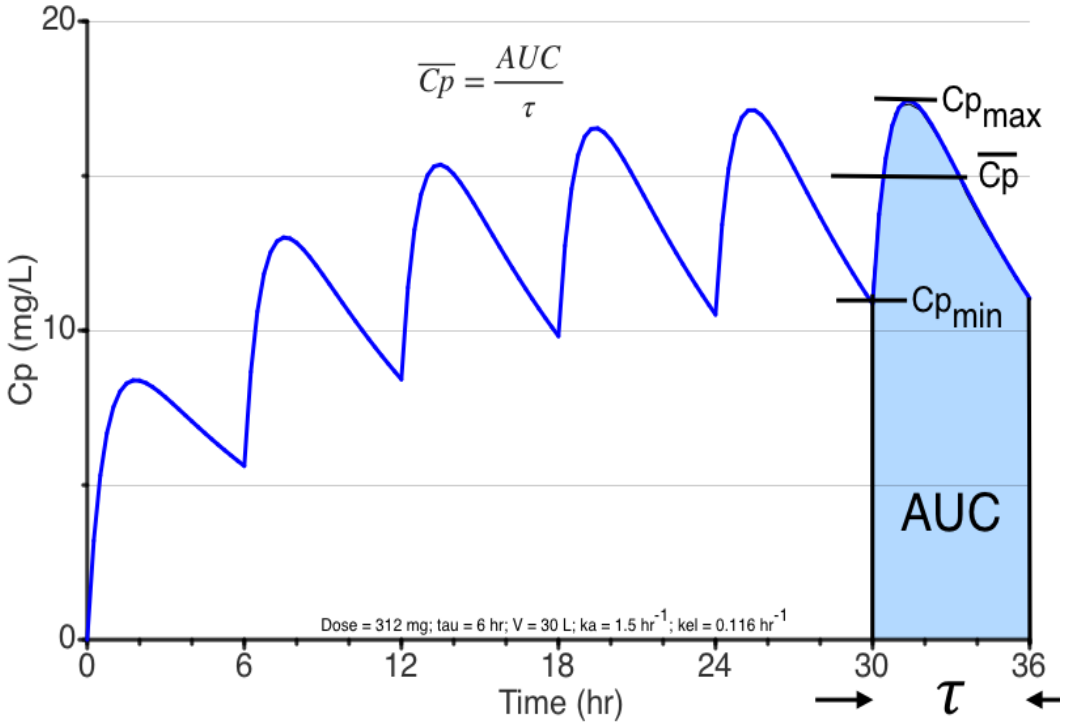
- Cavg can be the best alternative to dynamically varying inhibitor concentration (as shown by many publications)

PBPK: does dynamic [I]g & [I]h contribute to better accuracy?

- Dynamically varying [I] is not necessary for estimating AUCR, a non-dynamic measure of DDI risk.
- Accuracy of dynamically varying [I]g & [I]h in PBPK cannot be verified due to lack of IV data and non-identifiability of hepatic and gut contributions to DDI
- **Barriers to prediction accuracy:** Uncertainties in drug and system parameters common to both MSM and PBPK may play a bigger role in determining accuracy. **Investigational drug as precipitant:** Driver concentration for gut and transporter-mediated interactions cannot be verified. Uncertainty in interaction parameters. **Substrate:** Difficulty to characterize and quantify drug disposition pathways

Details - Back-up

Average steady state concentration



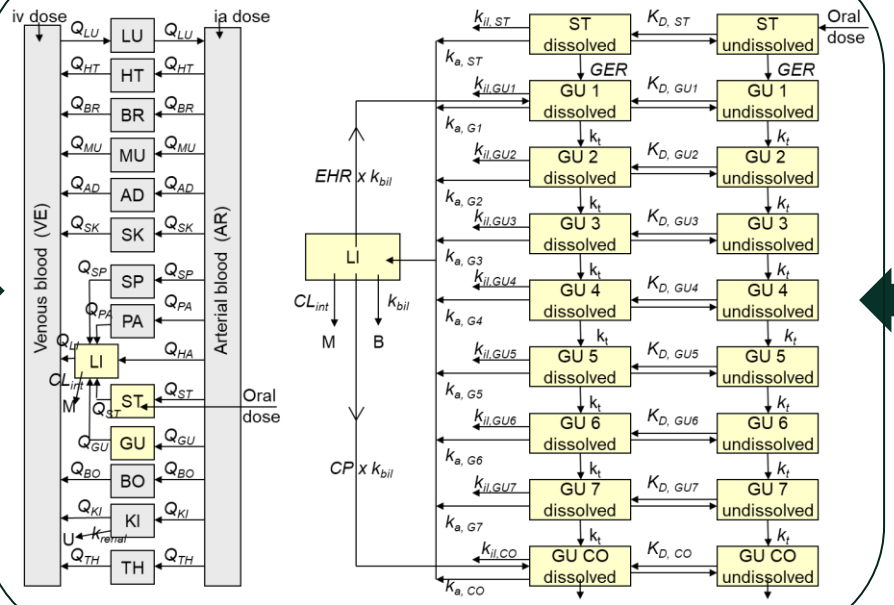
Prediction accuracy

Challenges to reliably source the critical parameters needed to build a robust model

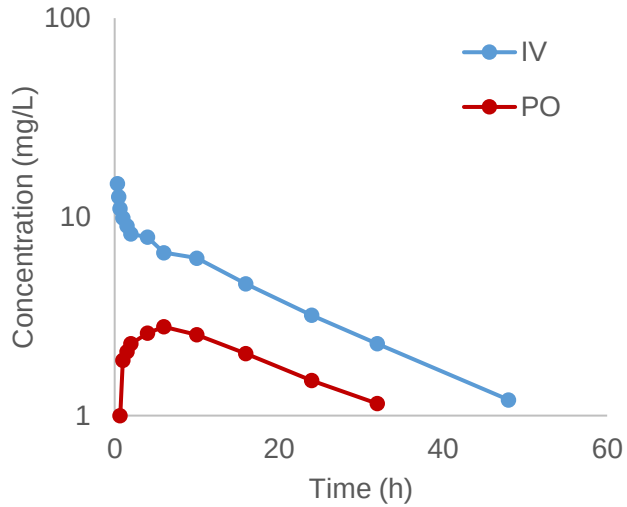
Bottom-up

- Solubility
- Dissolution
- Precipitation

PBPK model



Top-down



IVIV disconnect
Uncertainty in input parameters

Predictions may be misleading if model verification to confirm IVIVE or to validate assumptions is hampered by non-identifiability that cannot be resolved through clinical data for an intended use

Non-identifiable mechanisms underlying oral PK profiles
Non-identifiability of transporter and metabolism-mediated hepatic clearance

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Transporter-mediated DDI

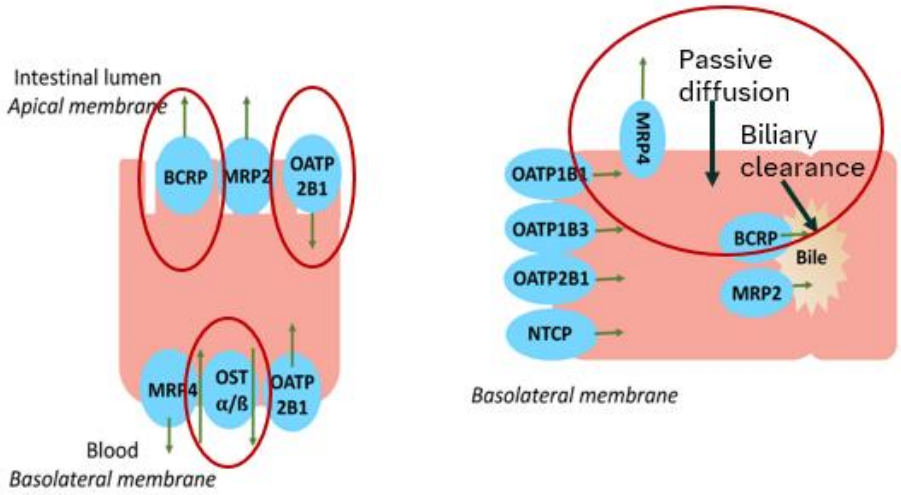
Prediction of DDI between rosuvastatin and OATP inhibitors

When simplicity can serve the purpose better

PBPK: 5 models for rosuvastatin (Bowman et al, CPT:PSP 2021)

- CLh (IV PK) available; Vss: 0.117 – 0.7
- Assumes in vitro data for transporters is quantitative (RAF = 1)

Different non-identifiable (unverified) drug disposition pathways parameterized differently fit observed data equally well



Hepatic

- Passive diffusion
- Uptake (in vitro scaled, RAF =1)
- With or without OATP2B1
- MRP4 & biliary CL
- Additional CL(retrograde)

Intestinal:

- Peff: 0.036 – 0.855
- With/without dissolution
- BCRP (model-fit Jmax/CLint),
- Apical uptake /basolateral OST fit assuming delayed absorption rate is transporter-driven

MSM vs. PBPK

3

MSM

Parameters:

- fT,BCRP: fostamatinib DDI study
- fT,OATP1B1/3: phenotyping

Assumption:

- CLh is entirely driven by OATP & NTCP uptake (in vitro) - worst case scenario

Simplicity of MSM enables timely conservative estimates for decisions on need & timing of DDI study

PBPK

- PBPK aims to include all known mechanisms and data but with many assumptions
- Model description, parameterization - subjective
- Sourcing parameters can be error prone
- Model verification to validate assumptions in characterizing drug disposition or to build confidence in IVIVE hampered by non-identifiability even for rosuvastatin (lots of data, many academic/ industry scientists working for many years (>13 yrs)
- Clinical DDI for verifying models may be inadequate

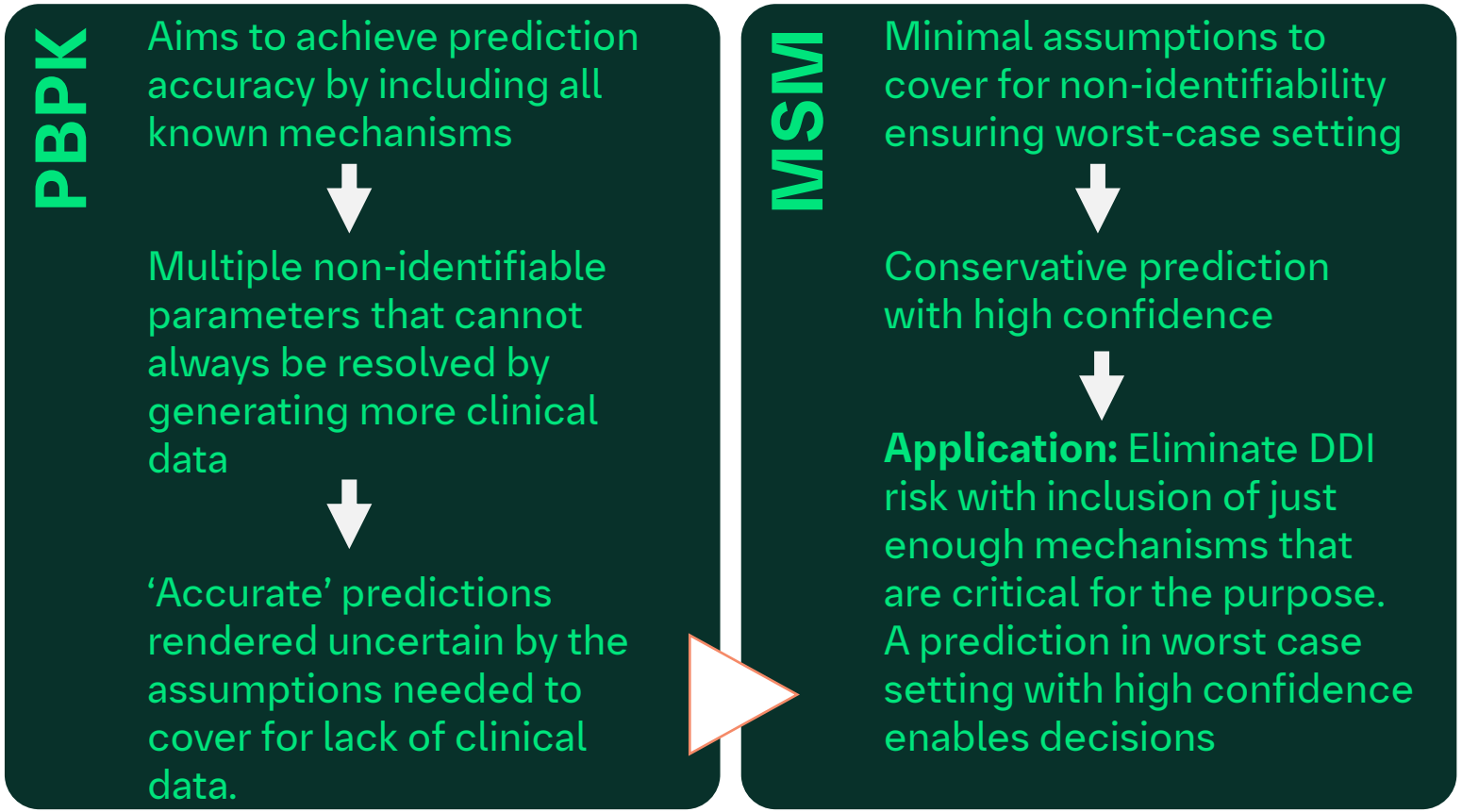
Clinical DDI used for PBPK model verification

Inhibitor	Transporter inhibited
Cyclosporine	OATP1B1/3, BCRP, NTCP
Rifampicin (IV & PO)	OATP1B1/3, BCRP
Gemfibrozil	OATP1B1/3, OAT3

Details – Back-up

MSM prediction under worst case to cover for non-identifiability

When non-identifiability cannot be resolved through data generation in the clinic, MSM predictions under worst case scenario to cover for assumptions makes mispredictions less likely



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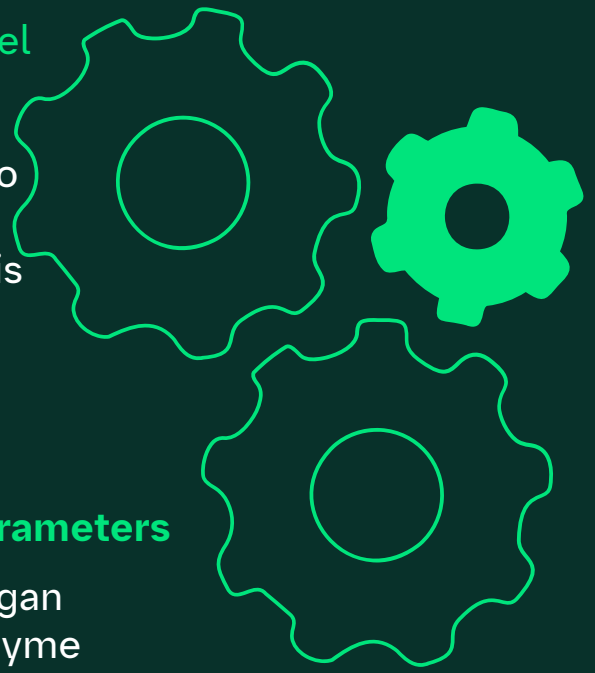
PBPK: Challenges today

When scientifically well-founded, the mechanistic basis of PBPK can help reduce the uncertainty and increase confidence in extrapolations outside the studied scenarios or studied populations.

Drug: Building mechanistically credible model

1. Characterization of drug disposition.
2. Model verification to validate assumptions, to confirm IVIVE or to build confidence in the proposed hypothesis to explain observation is hampered by non-identifiability



Time

1. Model development
2. Review timelines

Resource intensive

System parameters

Ontogeny, impact of disease / organ impairment on physiology on enzyme expression are often not well-understood

Predictive models for DDI prediction

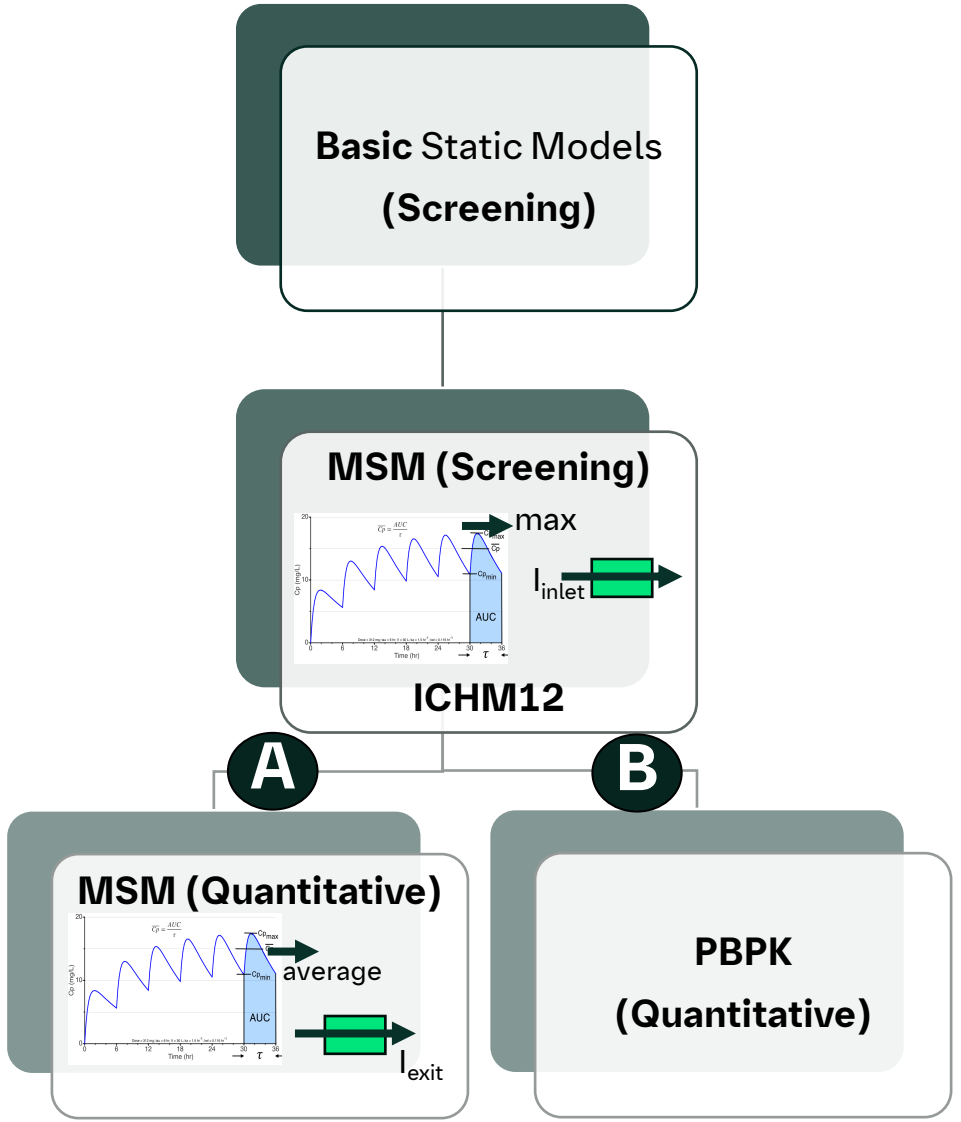
Opportunity to choose PBPK or MSM for quantitative predictions, considering the strengths of each for an intended use

A **MSM** (fast, minimal assumptions)

- enable timely decisions and submissions to agencies
- estimate AUCR under worst case scenario to cover for assumptions/non-identifiability and uncertainties in input that cannot be resolved/verified through clinical data.

B **PBPK** (Cmax ratio estimation and population extrapolation)

- there is unique value addition by PBPK for an intended use (e.g., Cmax ratio is considered important, population extrapolation)
- a mechanistically credible model for an intended use can be built (no ambiguity in metabolic/elimination pathways) and verified
- there is a high probability of success (~50% of submissions to FDA were successful in waiving studies/informing labels)



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Proposal

A pragmatic approach to applying predictive modelling

Early Development

Internal decisions: do we need a DDI study? If yes, when?

Mechanistic static model (MSM)

Phase II

Design DDI study to maximize interactions, design PoC study for broader permitted comedications, determine need for dose adjustment with comedications, if needed

MSM or PBPK depending on intended use

NDA submission

Predict unstudied scenario for study waiver & labelling: DDI at a different registrational dose of precipitant (P) to one in DDI study, impact of P on repeat dosing of a substrate that is inducer/ TDI, fill info gaps for difficult to recruit populations

PBPK and MSM

A routine comparison of PBPK and MSM, adopting the same workflow & data could help identify mechanistic gaps in PBPK, provide valuable learning and enable optimal use of models in the future

Key takeaways

1. Use of maximum, organ entry [I] in MSM, recommended in guidelines, overestimate DDI. Use of average, organ exit concentration of precipitant in MSM provide quantitative predictions comparable with those from PBPK

2. In both models, prediction accuracy is limited by the same factors - uncertainty in interaction parameters (precipitant) or difficulty to characterize drug disposition such as fT, fgut (substrate).

3. Model predictions from MSM and PBPK are **not comparable when there are non-identifiability issues** originating in the gut (eg, ibrutinib) or liver (eg, rosuvastatin).

4. When model verification to confirm IVIVE, validate assumptions /hypotheses is hampered by non-identifiability, predictions to untested scenario can be misleading

5. When non-identifiability cannot be resolved through data generation in the clinic, MSM predictions under worst case scenario (or with sensitivity analysis) could be an alternative, since assumptions are minimal and mispredictions are less likely.

6. A routine comparison of PBPK and MSM, adopting the same workflow and input data for interacting drugs can provide valuable learning and enable optimal use of models in the future.

Back-up

Mechanistic Static Models(MSM)

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Mechanistic Static Models(MSM)

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Mechanistic Static Models (MSM)

Reversibe CYP inhibition

$$\frac{AUC_i}{AUC} = \frac{f_{gut}^i}{f_{gut}} \times \frac{1}{\sum_i^n \left(\frac{f_m \times f_{m,CYP}}{1 + \sum_j \frac{I_u}{K_{i,u}}} \right) + (1 - \sum f_m \times f_{m,CYP})}$$

TDI

$$\frac{AUC_i}{AUC} = \frac{f_{gut}^i}{f_{gut}} \times \frac{1}{\sum_i^n \left(\frac{f_m \times f_{m,CYP}}{1 + \sum_j \frac{k_{inact} \times I_u}{k_{deg} \times (K_{I,u} + I_u)}} \right) + (1 - \sum f_m \times f_{m,CYP})}$$

Induction

$$\frac{AUC_i}{AUC} = \frac{f_{gut}^i}{f_{gut}} \times \frac{1}{\sum_i \left(f_m \times f_{m,CYP} \times (1 + \sum_j \frac{E_{max} \times I_u}{EC_{50} + I_u}) \right) + (1 - \Sigma f_m \times f_{m,CYP})}$$

AUC_i = AUC of object when inhibitor is present
AUC = AUC of object in the absence of inhibitor
f^i_{gut} = fraction escaping gut metabolism in the presence of inhibitor
f_{gut} = fraction escaping gut metabolism in the absence of inhibitor
f_m = fraction of total elimination due to hepatic metabolism
$f_{m,CYP}$ = fr. of total hepatic metabolism due to a specific CYP
I_u = unbound inhibitor concentration
$K_{i,u}$ = unbound inhibitor constant

$K_{I,u}$ = unbound inhibitor concentration at 50% k_{inact}
k_{inact} = maximal enzyme inactivation rate constant
k_{deg} = endogenous degradation rate constant of enzyme

i: summation over CYP enzyme
j: summation over each inhibitor/inducer

References

1. Inhibition: Obach, RS. Curr Opin Drug Discov Dev, 2009, 12 :81
2. Induction: Almond, LM. et al, Curr Drug Metab 2009, 10:420

Transporter-mediated DDI

Mechanistic Static Models

$$\frac{AUC_i}{AUC} = \frac{1}{\frac{f_T}{1 + \frac{I_u}{K_{i,u}}} + (1 - f_T)}$$

→ renal uptake

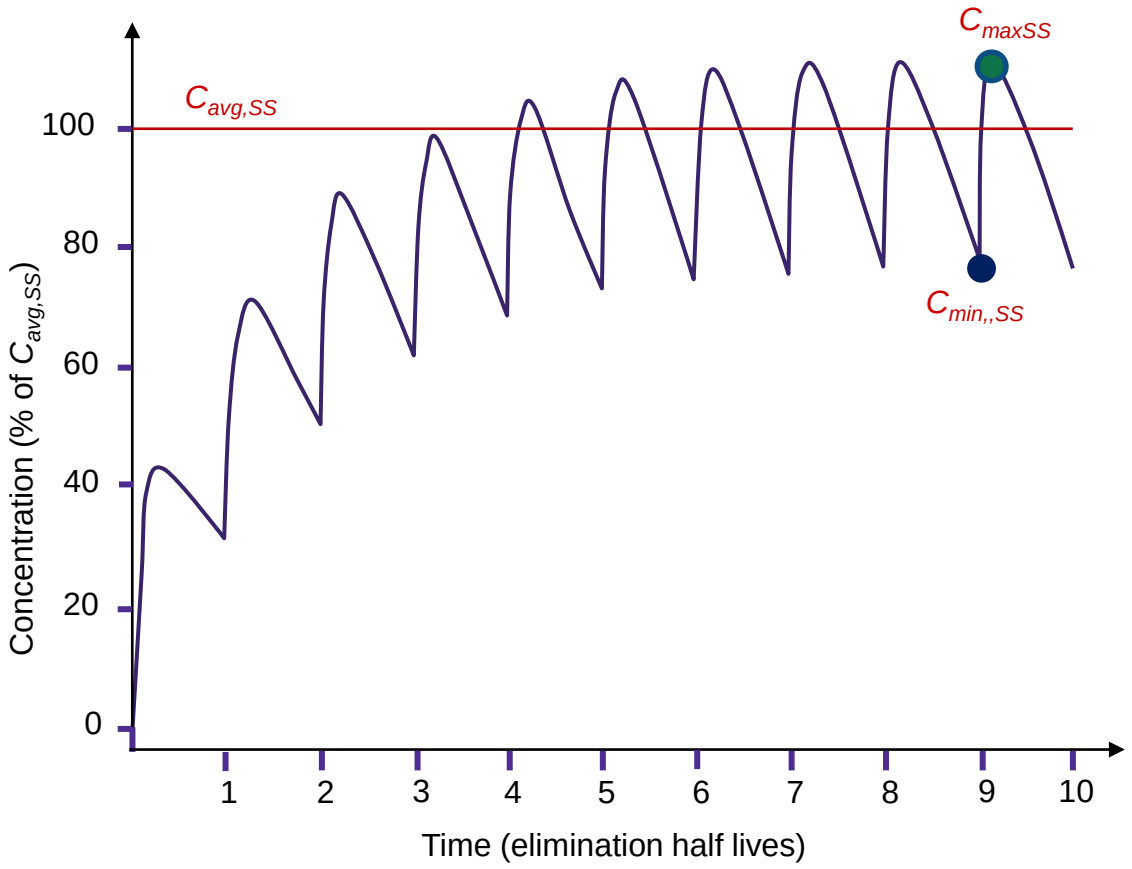
AUC_i = AUC of object when inhibitor is present
AUC = AUC of object in the absence of inhibitor
f_T is the fraction of clearance of the substrate (object), caused by a hepatic uptake transporter
$K_{i,u}$ is the inhibition constant measured in vitro corrected for binding to media

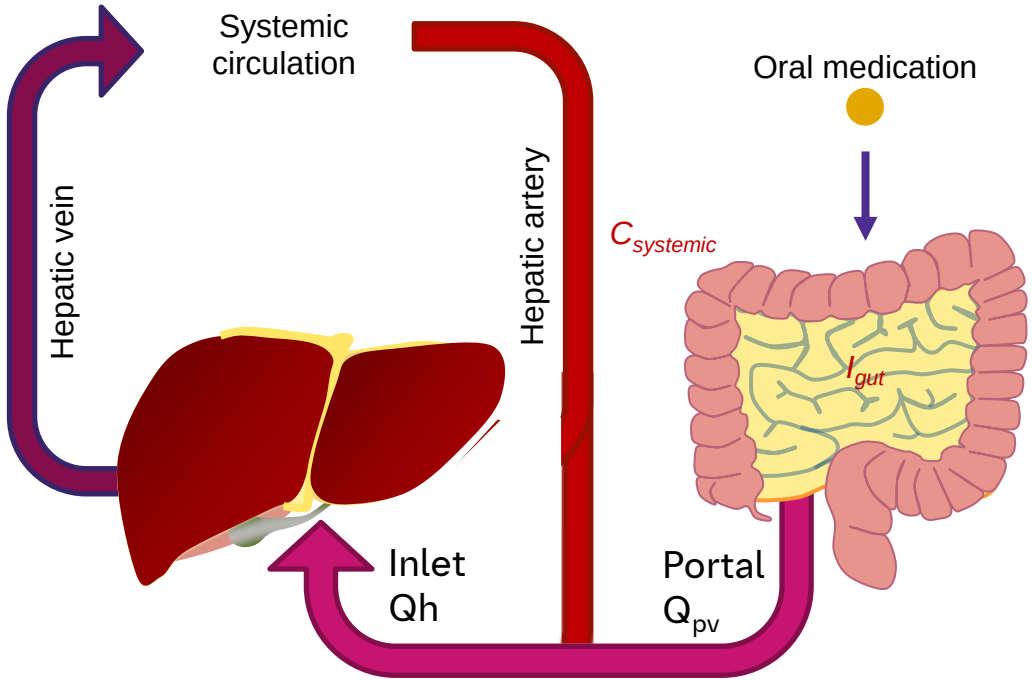
$$= \left(\frac{1}{\frac{f_{e,BCRP}}{1 + \frac{[I_{g,max}]}{IC_{50}}} + (1 - f_{e,BCRP})} \right) \times \left(\frac{1}{\sum \frac{fe,OATP1B}{1 + \frac{[I_{in,u,max}]}{IC50}} + (1 - \sum f_{e,OATP1B})} \right)$$

→ intestinal efflux and hepatic uptake

Reference: Obach RS. Predicting drug-drug interactions from in vitro drug metabolism data: Challenges and recent advances. *Curr Opin Drug Discov Devel*. 2009;12(1):81-89.

Drug as precipitant of DDI: Drug concentrations





$$I_{avg,portal,u} = \left[C_{avg} + \frac{\text{Dose} \times f_a \times f_g}{\tau \times Q_{pv} \times RB} \right] \times f_{u,p}$$

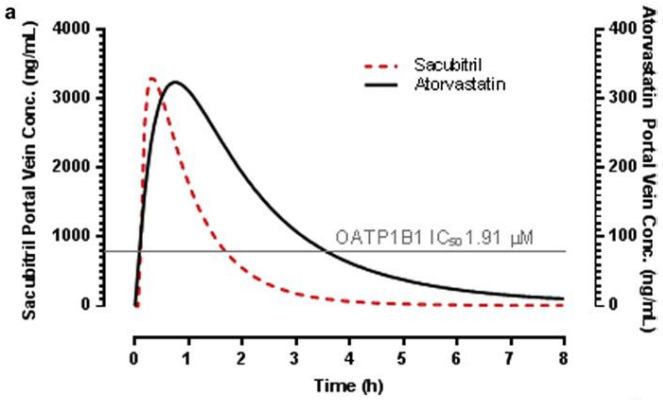
$C_{avg,SS}$, $C_{max,SS}$, $C_{min,SS}$ are systemic average, maximum and minimum inhibitor steady state concentrations respectively.
I_{gut} is the intestinal luminal inhibitor concentration, a surrogate for enterocyte concentrations
I_{portal} is the portal vein inhibitor concentration of an orally administered inhibitor.
f_a is the fraction of dose absorbed; f_g is the fraction of absorbed dose escaping intestinal loss by efflux and/or gut metabolism;
$f_{u,p}$ is the fraction of drug unbound in plasma; and Q_{pv} is the blood flow to hepatic portal vein.

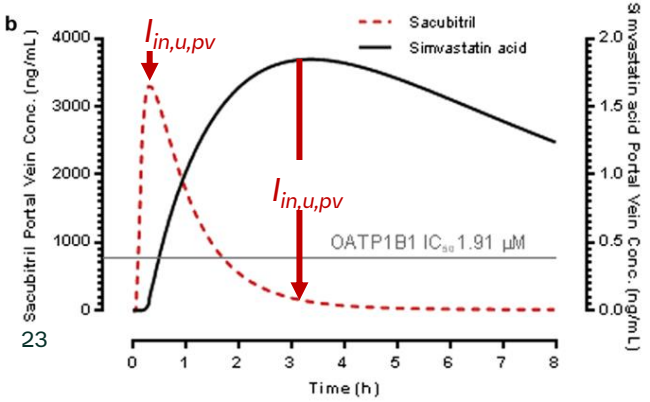
PBPK to explore differences in the extent of DDI for simvastatin and atorvastatin following inhibition of OATPs by sacubitril. Lin, J Ph Sci, 2017; 106:1439-51

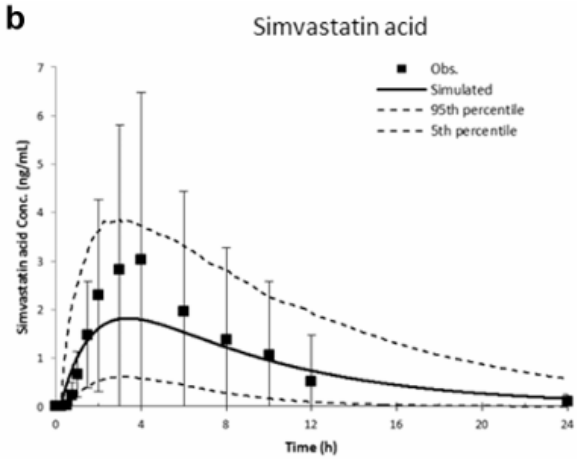
Observation

Simvastatin (prodrug lactone) —CES-1 in gut, plasma esterase→ Simvastatin acid (active SVA) —OATPs→ sacubitril **No DDI**

Atorvastatin —OATPs→ sacubitril **AUCR =1.3** **CmaxR = 1.7**







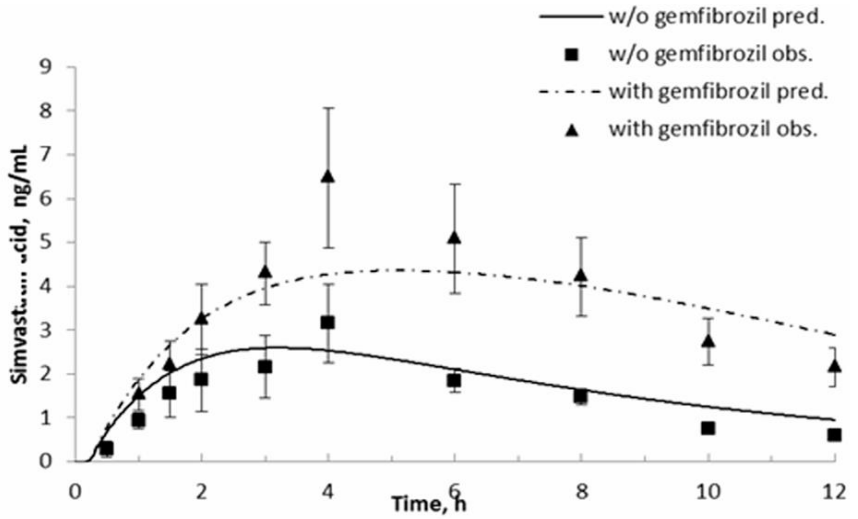
MSM to explore time function of DDI

1. Sacubitril

- Derive in vivo IC50 clinical DDI with atorvastatin
- Calculate a range of sacubitril concentration [I] at various time points until tmax of simvastatin

$I_{in,u,pv} = f_{u,p} \times (I_{systemic} + (Fa \times Fg \times Dose)/\tau/Qpv/RB)$

2. Simvastatin fe,OATP from its DDI with gemfibrozil



3. Predict sacubitril – simvastatin DDI

Calculate AUCR for the range of sacubitril [I]

$$AUCR = \frac{1}{\sum \frac{fe,OATP1B}{1 + \frac{I_{in,u,pv}}{IC_{50}}} + (1 - \sum fe,OATP1B)}$$

Barriers to prediction accuracy are common to MSM and PBPK

Type of DDI	Investigational drug	Bottom up: Uncertainty in critical drug parameters	Top-down modelling: Clinical data needed to verify model/confirm IVIVE Non-identifiability can sometimes hamper model verification / confirmation of IVIVE	Knowledge gaps in system parameters / Comments
CYP3A (low CL, negl. gut first pass) & other CYPs	Inhibitor	[I]systemic, interaction params (Ki, KI, kinact, EC50)	Clinical DDI study with sensitive substate →	One DDI study to optimize one interaction parameter. **TDI, induction:** it is possible to use differences in the extent of interaction after 1st dose and at SS to optimize parameters. Precipitant is both TDI and inducer: parameters are non-identifiable
	Substrate	fm, fm,CYP	Mass balance	
CYP3A (high CL, large gut first pass extraction)	Inhibitor	[I]gut [I]systemic, interaction params (Ki, KI, kinact, EC50)	Clinical DDI study with sensitive substrate administered IV and oral are needed	
	Substrate	fm, fm,CYP, fg	**Non-identifiable** gut/hepatic 1st pass without IV or mass balance	
Renal uptake (eg, OAT3)	Inhibitor	[I]systemic, Ki	Clinical DDI study with sensitive substrate	
	Substrate	PBPK: $CL_{int,transporter}$ MSM: fT	Renal clearance	
Basolateral hepatic uptake (eg, OATP1B)	Inhibitor	[I]portalvein, Ki	Clinical DDI with substrate	
	Substrate	PBPK: $CL_{int,enz}$, $CL_{int,transporter}$ MSM: fT	**Non-identifiable** contributions of enzyme and transporter to hepatic clearance; clinical DDI with inh	Scaling factors
Efflux transporters (eg, P-gp, BCRP)	Inhibitor	PBPK: $[I]_{intracellular}$, Ki MSM: organ exit: Cavg and Cavg,pv (**?**), Ki	**Non-identifiable:** 2 uncertain parameters cannot be optimized with only plasma drug concentration; clinical DDI study with substrate	
	Substrate	PBPK: $CL_{int,enz}$, $CL_{int,transporter}$ MSM: fT	**Non-identifiable** pathway contribution of transporter to elimination in gut, liver/kidney; clinical DDI with inh	Scaling factors

Prediction accuracy – MSM and PBPK

Enzyme-mediated DDI

Prediction accuracy

Drug as precipitant of DDI: Interaction Parameters

Reversible inhibition

Ki: in vitro, sensitivity analysis of 10-fold lower value to cover for inter-lab differences

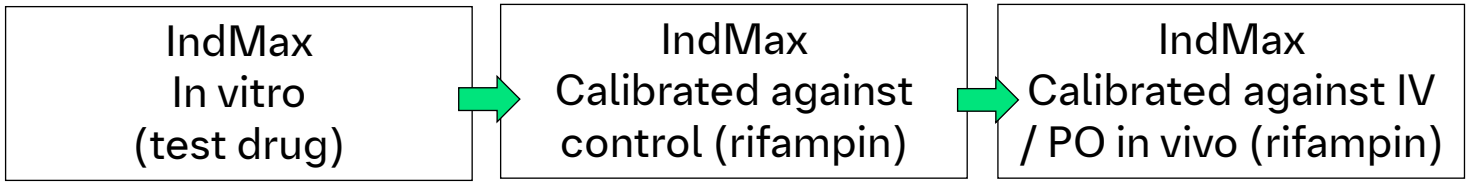
Time-dependent inhibition

KI: in vitro, sensitivity analysis of 10-fold lower value to cover for inter-lab differences

Kinact: in vitro

Induction

IndMax



IndC50

- **If test drug is inducer and sensitive substrate of the same enzyme:** Derived from the autoinduction effects observed in repeat-dosing studies at multiple doses
- **Otherwise,** in vitro

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Prediction accuracy

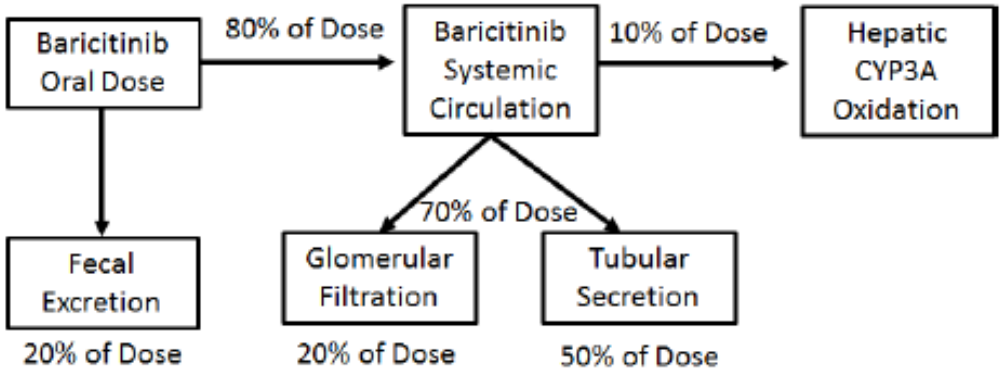
Drug as object of DDI: Pathway characterization

GUT	LIVER	KIDNEY
Fraction absorbed f_{abs}	Fraction eliminated in bile f_b	Fraction eliminated in urine f_e
Gut metabolism Fraction escaping gut metabolism, f_g	**Hepatic metabolism** Enzyme phenotyping: $f_{m,isofom,liver}$ for CYPs, UGTs, etc	

Transporter substrate

- In vivo relevance of uptake transporters in aiding absorption or metabolism through enzyme-transporter interplay
- In vivo relevance of different efflux transporters in determining gut bioavailability, biliary and renal elimination in vivo

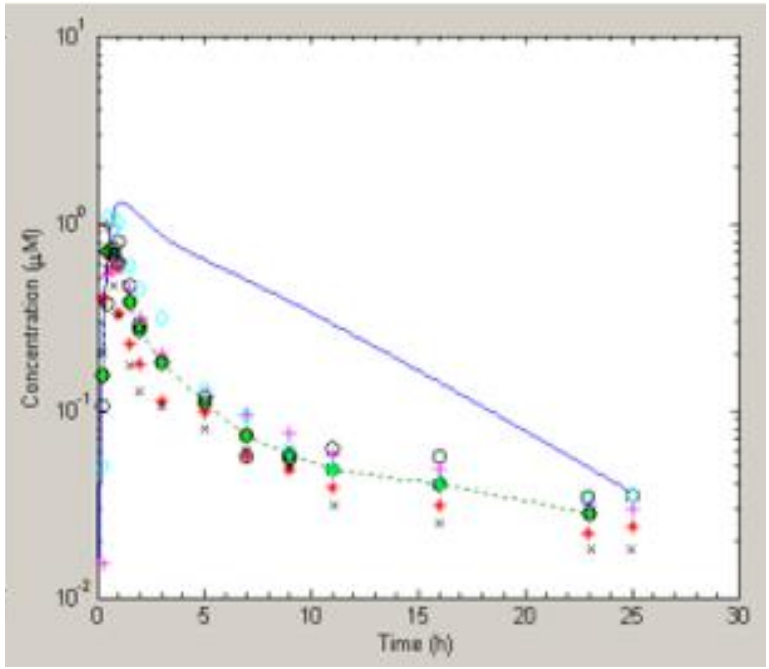
Example: Mass balance diagram



Prediction accuracy

Non-identifiability of mechanisms underlying oral PK profiles

When model simulated profile does not fit the observed, we may need to optimize the model parameters.
But which one?



- Gut metabolism?
- Efflux?
- Solubility/dissolution-limited absorption?
- Precipitation?

- Different model parameter combinations of these processes can describe observed data equally well
- Assumptions (based on in vitro data) on mechanisms relevant to molecule of interest may be necessary
- **Consequence of non-identifiability:** PBPK models that show excellent fit to one set of observed data may lack sound mechanistic basis to predict an untested scenario.

Enzyme-mediated DDI

Comparison of PBPK and MSM (CYP3A rev inhibition)

EJ Guest et al, BJCP 2011

Dynamic (●) or static (▽) model in Simcyp v8. Horizontal dashed lines: 2-fold margins. Vertical dashed lines: boundaries between weak (W), moderate (M) & strong (S) DDI

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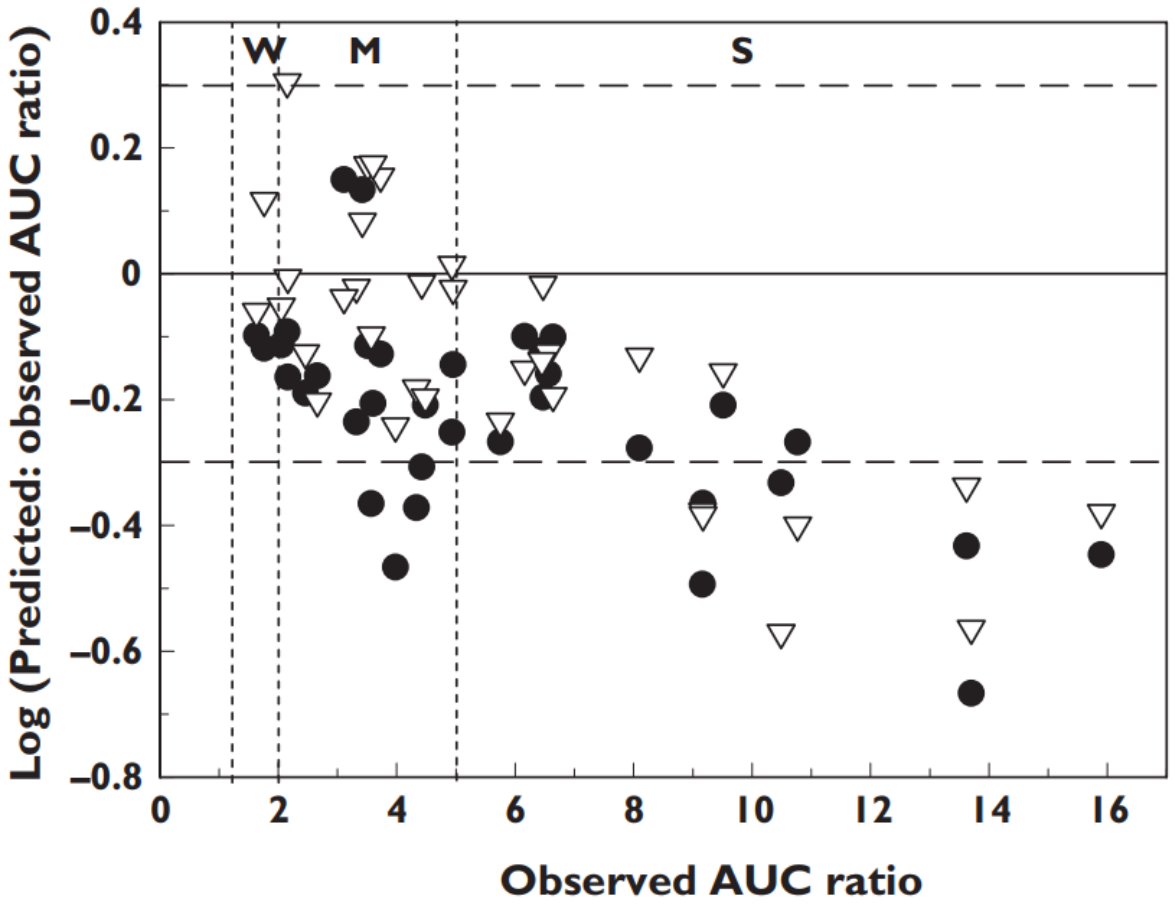
Azole inhibitors



- Steady state unbound average concentration
- Good overall prediction of DDIs investigated observed using both models with **71% (PBPK)** and **77% (MSM)** of studies within 2-fold of the observed AUC ratio, respectively

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Enzyme-mediated DDI

Comparison of PBPK and MSM (CYP3A, TDI)

E Tseng et al, DMD 2021

Current Guideline

Best prediction accuracy

	C_{max},entrance	$C_{max,u}$, entrance	$C_{max,u}$, exit	$C_{avg,u}$, exit
	Model 1	**Model 2**	**Model 3**	**Model 4**
k_a	0.1 min^{-1}	custom	custom	custom
$[I]_g$	Total Enterocyte[a]	Free Enterocyte[b]	$C_{max,portal,u}$[c]	$C_{avg,portal,u}$[d]
$[I]_h$	$C_{max,hepatic\ inlet,u}$[e]	$C_{max,hepatic\ inlet,u}$[e]	$C_{max,systemic,u}$	$C_{avg,systemic,u}$
$f_{u,gut}$	1	$f_{u,plasma}$	$f_{u,plasma}$	$f_{u,plasma}$

[a/b]As calculated per equation 7a with/without correction for free fraction in plasma
[c]As calculated per equation 7b
[d]As calculated per equation 7c
[e]As calculated per equation 6

$$C_{max,hepatic\ inlet,u} = f_{u,p} \times \left(C_{max} + \frac{F_a \times F_g \times k_a \times Dose}{BPR \times Q_h}\right) \text{(eq. 6)}$$

$$[I]_g = \frac{F_a \times k_a \times Dose}{Q_{ent}} \quad \text{(eq. 7a)}$$

$$C_{max,portal,u} = f_{u,p} \times \left(C_{max} + \frac{F_a \times F_g \times k_a \times Dose}{BPR \times Q_{pv}}\right) \text{(eq. 7b)}$$

$$C_{avg,portal,u} = f_{u,p} \times \left(C_{avg} + \frac{F_a \times F_g \times Dose}{\tau \times BPR \times Q_{pv}}\right) \text{(eq. 7c)}$$

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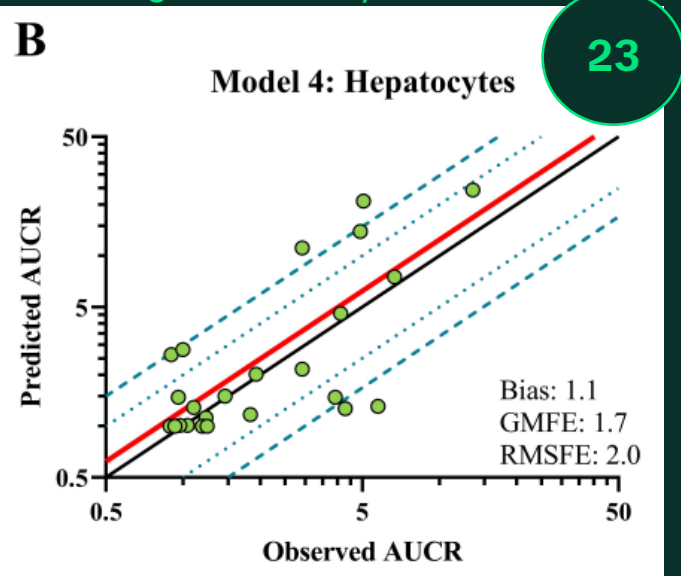
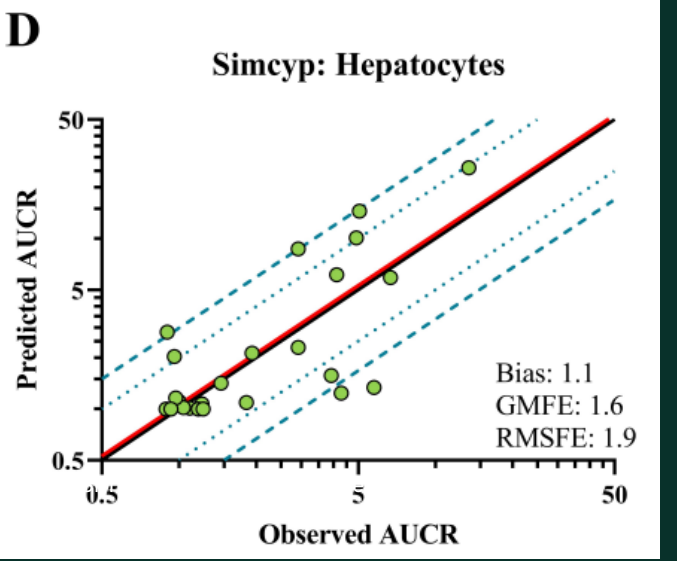
Lesser risk for false negatives with MSM (Model 4) relative to PBPK

Gut: Avg unbound portal conc

Liver: Avg unbound systemic conc



Similar results for HHLM; HHEP better than HHLM



Enzyme-mediated DDI

Assessment of Clinical DDI Risk (CYP3A Induction)

Ramsden and Fullenwider EJDMPK(2022)

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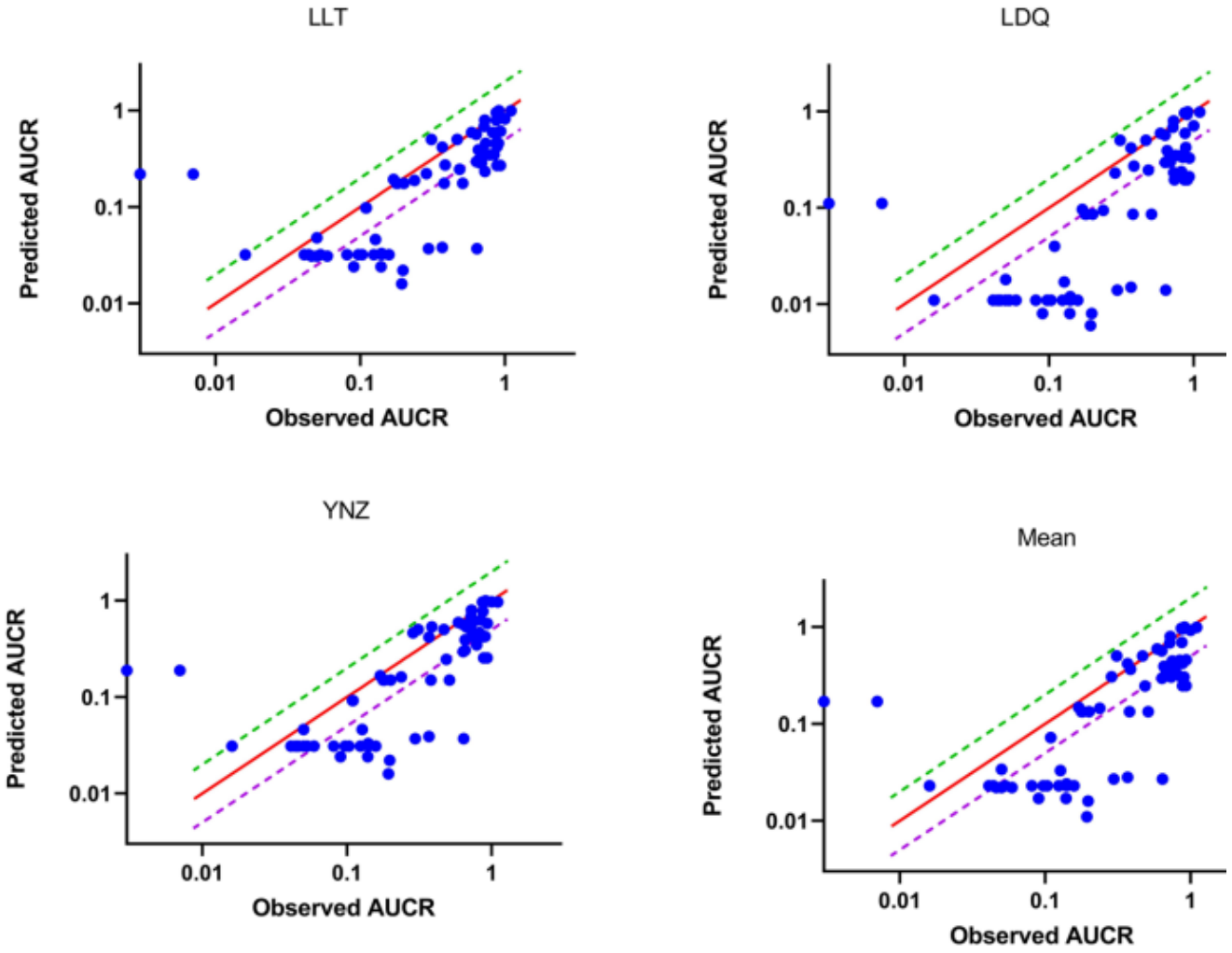

MSM predictions for 3 donors & avg donor induction parameters using Model 4 (best of 4)

Model 4
Gut: Avg unbound portal conc
Liver: Avg unbound systemic conc

$$C_{g,k} = \frac{1}{1 + \frac{d \times E_{max} \times I_{gut}}{I_{gut} + EC_{50}}}$$

$$C_{h,k} = \frac{1}{1 + \frac{d \times E_{max} \times I_{liver}}{I_{liver} + EC_{50}}}$$

d = 1

Induction parameters from

Kenny JR, et al Drug Metab Dispos. 2018;46(9):1285–303

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Prediction accuracy – MSM and PBPK

Transporter-mediated DDI

Transporter-mediated DDI

Precipitant concentrations for screening and quantitative predictions

Type of DDI	Sub-type of DDI	Screening (Draft ICH M12)	Quantitative predictions	Quantitative predictions -Comments | Reference
Transporter -mediated	Intestinal **(P-gp, BCRP)**	[I]g	**Proposed:** Gut: $C_{avg,portalvein}$	Large inter-lab variability in Ki reported for P-gp.
	Hepatic uptake **(OATP1B)**	[I]h	*Liver: [I]h = $C_{max,inlet}$	MSM and PBPK comparison for investigational drug as precipitant Sane et al, DMD (2020)
	Renal uptake **(OAT1/3)**	C_{max}	Observed C_{avg}	MSM and PBPK comparison for investigational drug as substrate Gomez-Mantilla et al, Clin PK (2023)
	Renal uptake & efflux **(OCT2, MATE)**			Krishnan et al, CPT (2022)

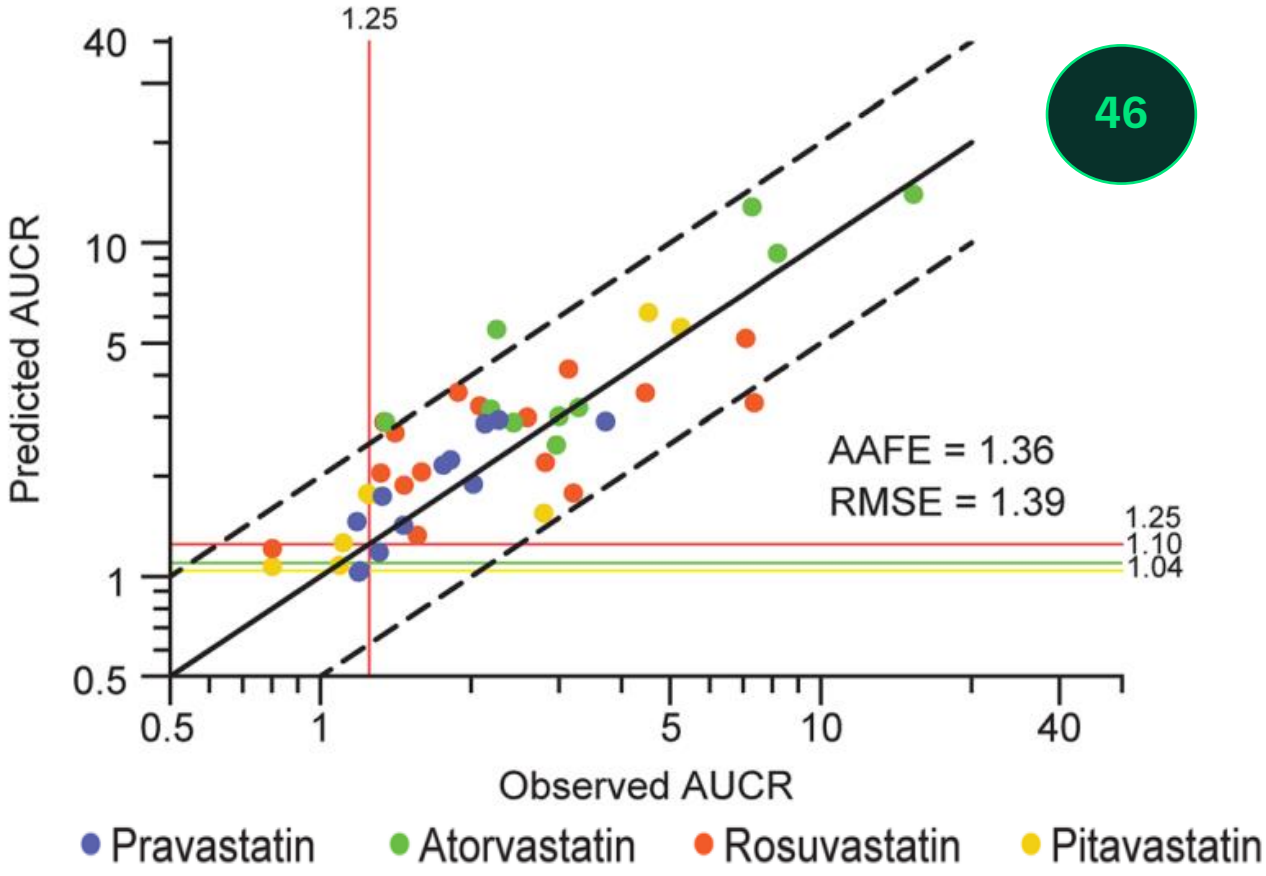
*Resulted in over-prediction. More realistic estimates may be possible with [I]h = $C_{avg,portalvein}$

Transporter-mediated DDI

Predicting statin DDIs with anti-viral drugs on multiple transporters, OATP1B, BCRP, MRP2, OAT3, and CYP3

Chu, X. et al, The AAPS Journal (2022)

- Inhibitory effects of 6 direct-acting antiviral drugs were evaluated in vitro using transporter transfected cells and membrane vesicles.
- Mechanistic models assessing differential inhibitory effects of precipitant drugs on multiple transporters, OATP1B, BCRP, MRP2, OAT3, and CYP3A successfully predicted a total of 46 statin DDIs, including 6 drugs and their fix-dose combination regimens



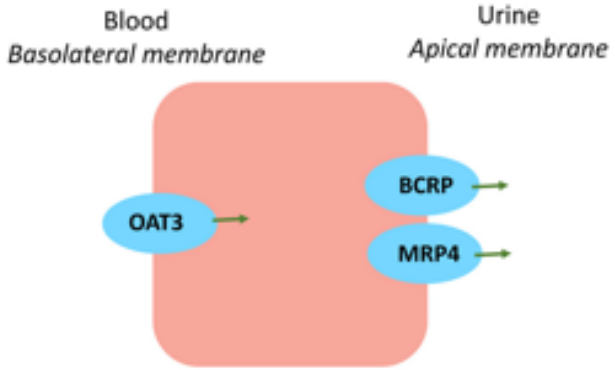
Transporter-mediated DDI

Baricitinib, a substrate of OAT3 among other transporters (MATE-2K, P-gp, BCRP)

Predict effect of OAT3 inhibition by moderate OAT3 inhibitors on baricitinib exposure

Insignificant decrease in renal CL of baricitinib with cyclosporin (P-gp, BCRP inhibitor)

Renal secretion clearance (CL) of baricitinib is mediated only by OAT3



$$\frac{AUC_i}{AUC} = \frac{1}{\frac{f_T}{1+\frac{I_u}{K_{i,u}}} + (1 - f_T)}$$

OAT3	Precipitant	Object of DDI	Comment	
Clinical DDI study	Probenecid (strong)	Baricitinib	Used to derive baricitinib fT	
Prediction	Ibuprofen (moderate) Diclofenac (moderate)	Baricitinib	PBPK MSM	Posada MM, CTS 2017 Gomez-Mantilla JD, ClinPK 2023

Transporter-mediated DDI

PBPK: Predict effect of moderate OAT3 inhibitors on baricitinib exposure

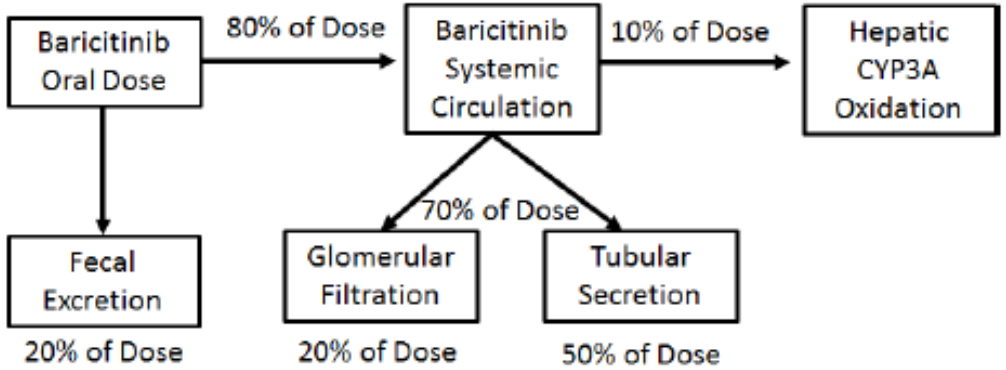
Posada MM, CTS 2017

Substrate: no additional scaling factor required to fit the active secretion	• Km, Vmax of baricitinib derived from transfected HEK cells. RAF = 1 was able to simulate observed renal CL.
Inhibitor: in vitro Ki = in vivo Ki = IC50	• In vitro IC50 values of probenecid, ibuprofen (probe, baricitinib) & diclofenac (probe, pemetrexed) were 4.41, 3.97 & 3.7 µM in transfected HEK cells expressing OAT3
Clinical DDI with strong inhibitor: Model simulates the 2-fold decrease in renal secretion of baricitinib	• Using *in vitro* IC_{50} value of 4.41 µM for probenecid
Model simulations with moderate inhibitors (ibuprofen and diclofenac) - clinically relevant DDIs unlikely	• Setting Ki=IC50 and Ki=IC50/2 in simulations to cover potential uncertainty in Ki estimation.
Label recommendation	• Dose adjustment with strong but not with moderate inhibitors

MSM: Predict effect of moderate OAT3 inhibitors on baricitinib exposure

Gomez-Mantilla JD, ClinPK 2023

Baricitinib parameters	
Total CL(L/h)	17
Renal CL (L/h)	11
fu,p	0.5
Blood plasma ratio (R)	1.26



1. Calculate the unknown parameter baricitinib f_T for OAT3

Method 1. Using clinical PK data (when only one uptake transporter is involved in DDI)

Renal CL of baricitinib due to filtration = fub*GFR = (fup/R)*GFR = (0.5/1.26)*7 L/h = 2.8 L/h

Renal CL of baricitinib due to transporter activity = 11 – 2.8 = 8.2 L/h

$$f_T = \frac{\text{Renal CL of baricitinib due to transporter activity}}{\text{Total CL of baricitinib}} = 8.2/17 = 0.48$$

Assumption
All transporter-driven renal CL is due to OAT3

Method 2. Using clinical DDI study (serves as verification)

Systematically vary f_T in MSM to predict the AUC ratio for the probenecid-baricitinib interaction, until the prediction matches the observed AUC ratio. f_T = 0.55

Assumption
in vitro Ki = in vivo Ki

2.Use the calculated baricitinib f_T to estimate the AUCRs for baricitinib interaction with the moderate inhibitors

Comparable prediction of AUCRs of baricitinib with OAT3 inhibitors by PBPK & MSM

Assumption: OAT3 is a unidirectional transporter

OAT3 inhibitor	PBPK	MSM Method 1 fT = 0.48	MSM Method 2 fT = 0.55
Probenecid 1000 mg BID Ki = IC50	**1.95**	1.79	**2.02**
Ibuprofen 400 mg QD Ki = IC50	1.14	1.14	1.16
Ibuprofen 800 mg QD Ki = IC50	1.24	1.24	1.28
Ibuprofen 400 mg QD Ki = IC50/2	1.35	1.38	1.46
Diclofenac 100 mg BID Ki = IC50	1	1	1
Diclofenac 100 mg BID Ki = IC50/2	1	1	1

Transporter-mediated DDI

Predict effect of OATP1B & BCRP inhibition on rosuvastatin exposure with MSM

Sane, R DMD, 2020

Rosuvastatin is a common comedication. Its disposition is mediated by both OATP1B1/3 in the liver and gut BCRP.

The effect of OATP1B and BCRP inhibition by drugs with potential to inhibit intestinal BCRP in vivo (Igut/IC50 > 10) on rosuvastatin exposure predicted using a combined static model. **In vitro systems for IC_{50}:** HEK293 cells overexpressing OATP1B1 or 1B3. Vesicles for BCRP inhibition

$$\text{AUCR (rosuvastatin)} = \left(\frac{1}{\frac{f_{e,BCRP}}{1+\frac{[I_{g,max}]}{IC_{50}}} + (1 - f_{e,BCRP})}\right) \times \left(\frac{1}{\sum \frac{fe,OATP1B}{1+\frac{[I_{in,u,max}]}{IC50}} + (1 - \sum f_{e,OATP1B})}\right)$$

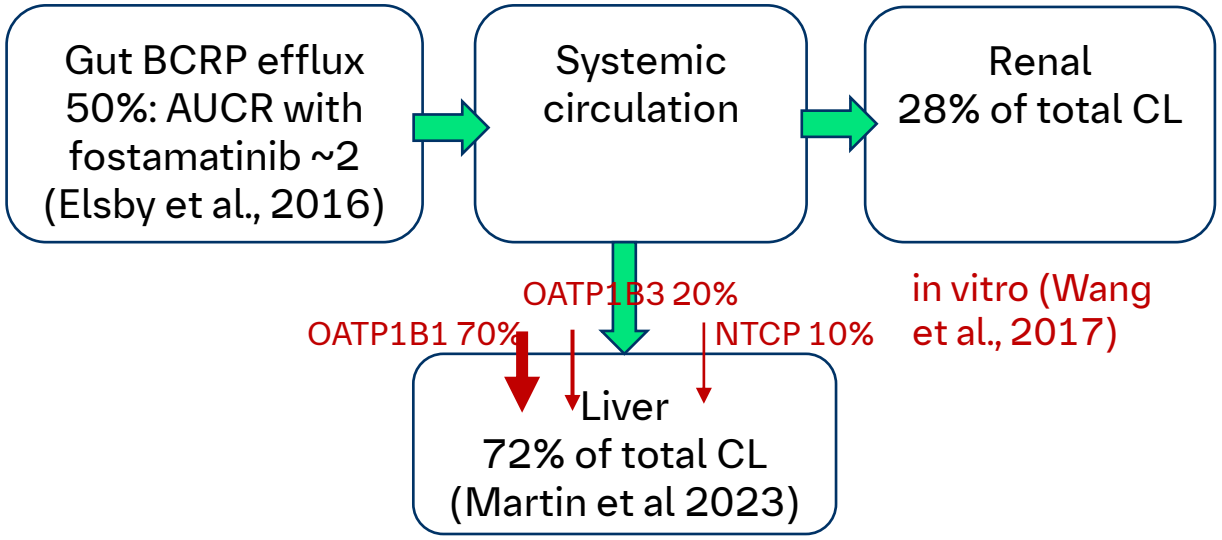
Combined model included only for OATP1B and BCRP inhibitors
when $[I]_{gut}(dose/250) > 10 \times IC_{50,BCRP}$

Transporter-mediated DDI

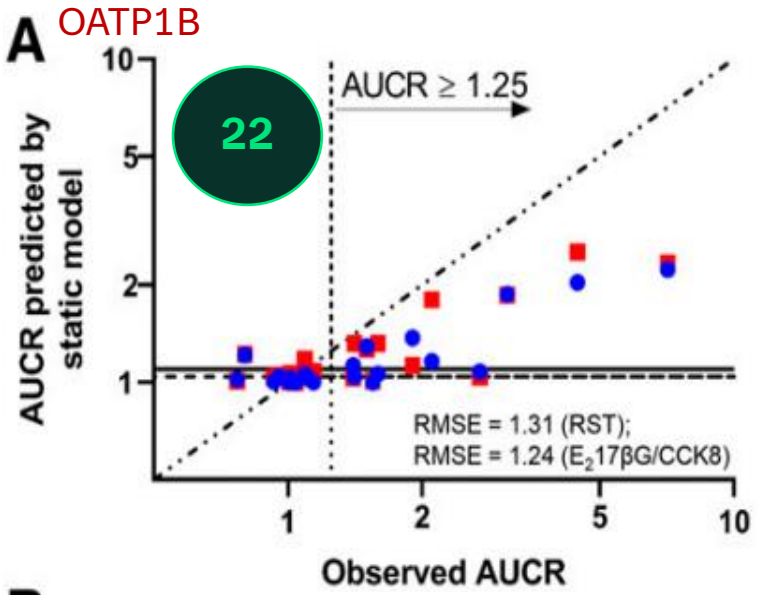
Predict effect of OATP1B & BCRP inhibition on rosuvastatin exposure with MSM

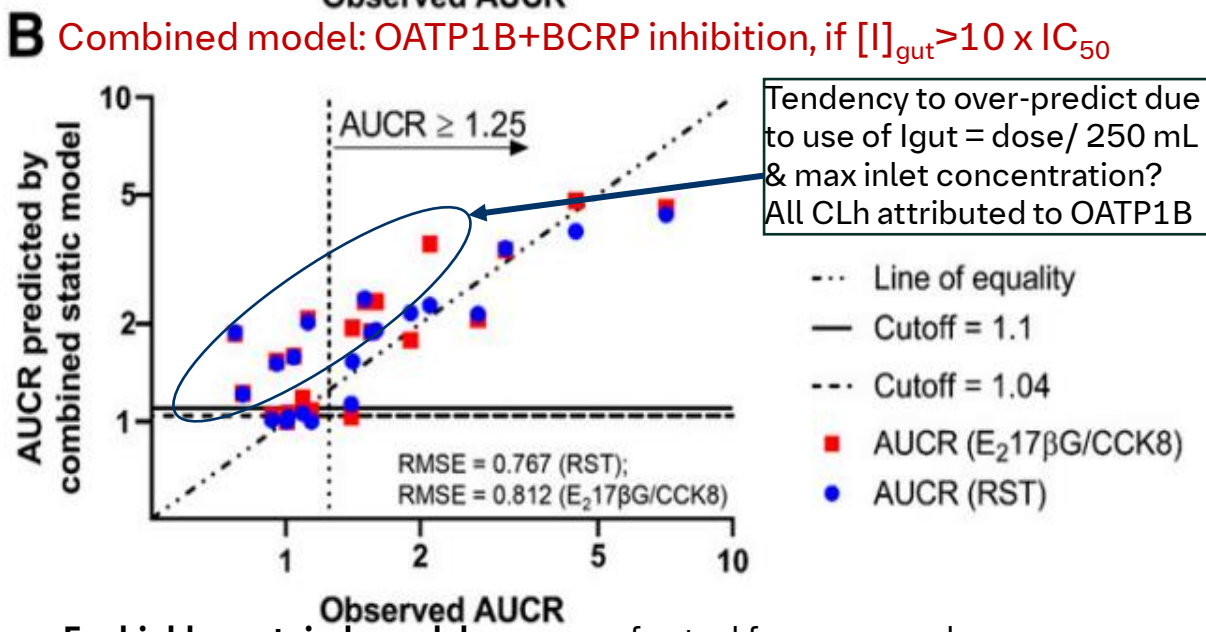
Sane, R DMD, 2020

Rosuvastatin disposition and estimated fT



Rosuvastatin: Estimated fT assuming hepatic CL is entirely driven by uptake (no passive transport): worst case scenario	
OATP1B1	0.504
OATP1B3	0.144
NTCP	0.072





For highly protein-bound drugs, use of actual fup or capped to 1% did not significantly impact predictions

Transporter-mediated DDI

Prediction of DDI between rosuvasatin and rifampicin, asunaprevir & velpatasvir

Comparison of static and PBPK models. Sane, R DMD, 2020

Rosuvastatin / E217βG or CCK as probe

	Observed	[1]PBPK	Static Model
Asunaprevir	1.41	1.3/1.9	1.53/1.94
Rifampicin	4.46	4.2/4.3	3.86/4.80
Velpatasvir (BCS IV)	2.69	1.4/1.3	2.14/2.06

Substrate-dependent scaling factors applied for experimental IC50 of OATP1B inhibitors for PBPK
Rosuvastatin: 200; CCK-8/E217βG: 100

Large, substrate-dependent scaling factors for IC50 needed only for PBPK

No hypothesis provided to explain the need for substrate-dependent scaling factors

Transporter-mediated DDI

Prediction with MSM and PBPK

	MSM	PBPK
Inhibitor	• $K_{i,u}$, optimized in vivo IC_{50} values recovered from clinical DDIs • I_u from clinical PK and protein binding data	• PK model building and verification • Bottom-up: $K_{i,u}$ • Middle-out: optimized in vivo IC_{50} values recovered from clinical DDIs
Substrate	f_T from clinical data (transporter-mediated elimination, pharmacogenetics, DDI studies)	Bottom-up: Km, Vmax, RAF/REF (default,1) used to build and verify PK model. RAF/REF is derived from clinical PK via simulation of transporter-mediated elimination

Challenges to predict tDDIs: high inter-lab variability of in vitro inhibition data for some transporters possibly due to differences in in vitro systems, probe substrates and assay conditions

Transporter-mediated DDI

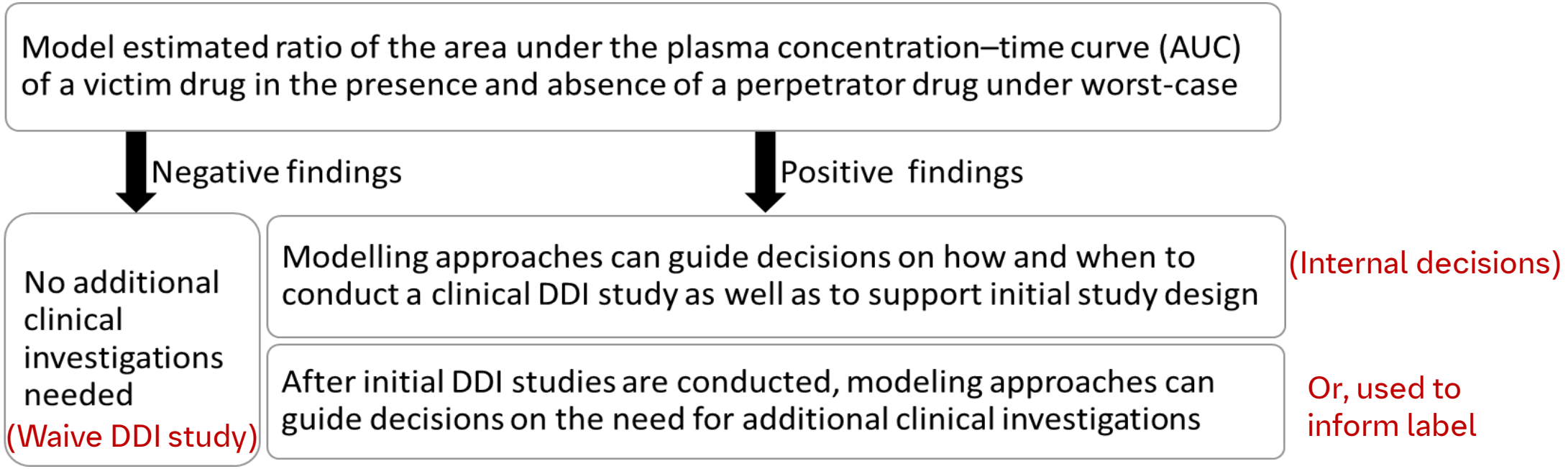
Summary of MSM use for different types of transporters

Type	Investigational drug as precipitant	Investigational drug as object of DDI
Intestinal efflux **BCRP, P-gp**	$C_{avg,portal,u}$? Ki of P-gp: high inter-lab variability	MSM may be possible • If compound behaves like BCS I • Low CL CYP3A substrate – no gut metabolism • Not a substrate of UGT or CYP3A • IV PK is available
Hepatic uptake **OATP1B1, OATP1B3**	$C_{avg,portalvein,u}$ (to be validated) Ki scaling factor 1 works in MSM	fT_{BCRP} (intestinal) from DDI study with fostamatinib fT for OATP1B1 from phenotyping, confirmed with clinical DDI study with OATP1B1 inhibitor **OR** fT (worst case) with all hepatic CL assigned to transporter for low CL drug
Renal basolateral uptake **OAT1, OAT3, OCT2**	$C_{avg,u}$ Ki scaling factor 1	Renal CL used to calculate fT if single transporter is involved. **OR** Use DDI with strong inhibitor to get fT.
Renal efflux **MATEs**	Rare. The renal uptake is mostly the rate-limiting step.	

Regulatory submissions - PBPK

Introduction

Predictive models: Eliminate DDI risk, guide decisions and support study design



Internal decision during clinical development

- Design study to maximize interactions
- Inform exclusion of concomitant medication
- Decide on need and timing of study

Regulatory

- Waive DDI study
- Inform label (dose adjustment, contraindication or no warnings)

Enzyme-mediated DDI

Reversible & time-dependent inhibition and induction

Reversible inhibition

- CYPs: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A
- UGTs: UGT1A1 and UGT2B7. UGT inhibition-mediated DDIs are generally of limited magnitude

Time-dependent inhibition

- CYPs: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A

Induction

- CYP3A4, CYP2B6 and CYP1A2 are markers of induction mediated via PXR/CAR (CYP3A4, CYP2B6) and AhR (CYP1A2). Evaluating the induction potential of a drug on CYP2C enzymes is not necessary because both CYP3A4 and CYP2C enzymes are induced via activation of the PXR. CYP2Cs are generally less inducible compared to CYP3A4. If investigational drug induces CYP3A4 in vitro, and the results suggest that a clinical study should be conducted, its potential to induce CYP2Cs should be evaluated in vitro and/or in vivo. Alternatively, a negative clinical study with a sensitive CYP3A substrate can be used to rule out the induction potential of an investigational drug on CYP2C enzymes if the potential of CYP3A inhibition by the drug and its metabolite(s) can be excluded via in vitro and/or in vivo evaluation. For CYP2C19, activity should be measured, as mRNA responses to inducers are often limited

Transporter-mediated DDI

Intestinal, hepatic and renal basolateral uptake & efflux

For a drug that is orally administered and/or if biliary excretion or active renal secretion is likely to be a major elimination pathway

- P-glycoprotein (P-gp)
- Breast Cancer Resistance Protein (BCRP)

Hepatic basolateral uptake

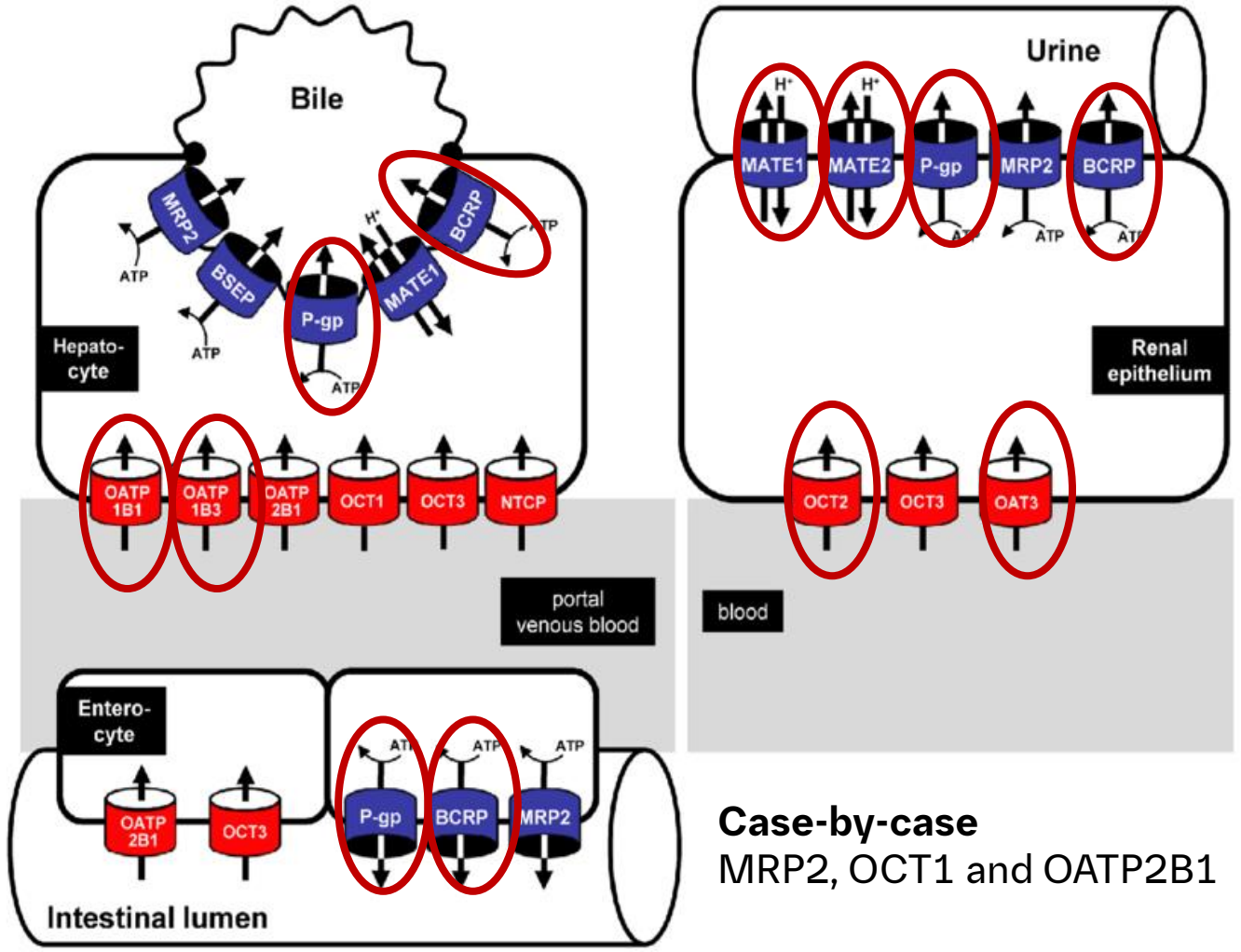
- Organic Anion Transporting Polypeptide (OATP1B1, OATP1B3)

Renal basolateral uptake transporters

- Organic Anion Transporter (OAT1, OAT3)
- Organic Cation Transporter (OCT2)

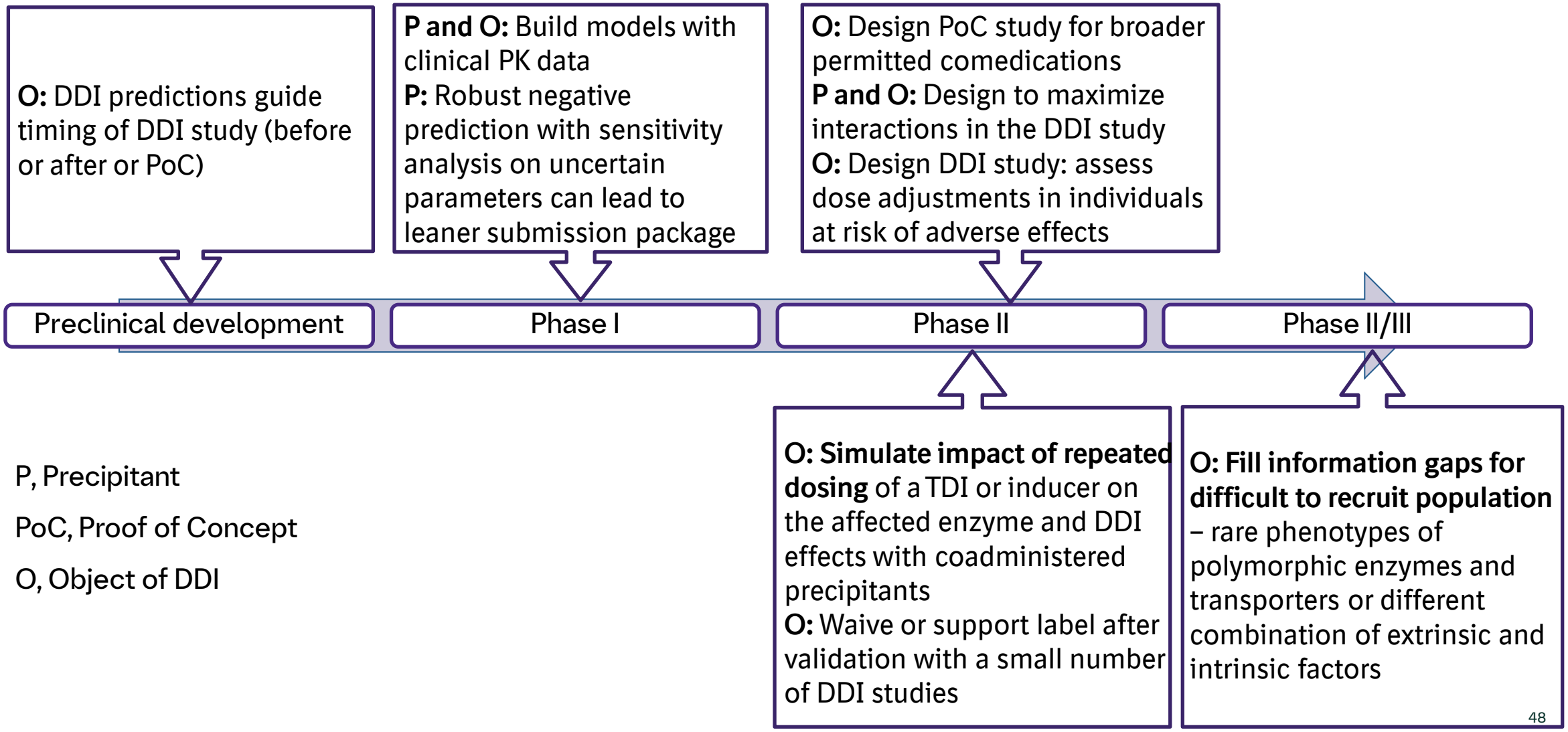
Renal efflux transporters

- Multidrug and Toxin Extrusion protein (MATE1, MATE2-K)



Case-by-case
MRP2, OCT1 and OATP2B1

Current applications of static and dynamic models for inhibition and induction DDI predictions across the discovery and development continuum



P, Precipitant

PoC, Proof of Concept

O, Object of DDI

PBPK submissions to OCP

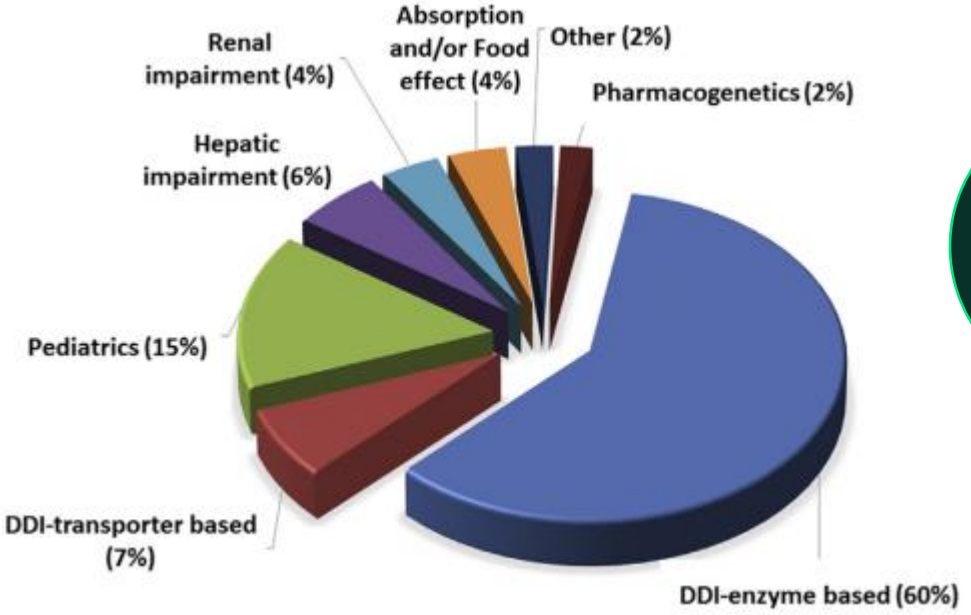
~50% deemed adequate

1

Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology

Manuela Grimstein, Yuching Yang*, Xinyuan Zhang*, Joseph Grillo, Shiew-Mei Huang, Issam Zineh, Yaning Wang

PBPK submissions from 2008-17: 254 total; 94 NDAs 72
DDI (52 enzymes). 26 informed label



50% success rate

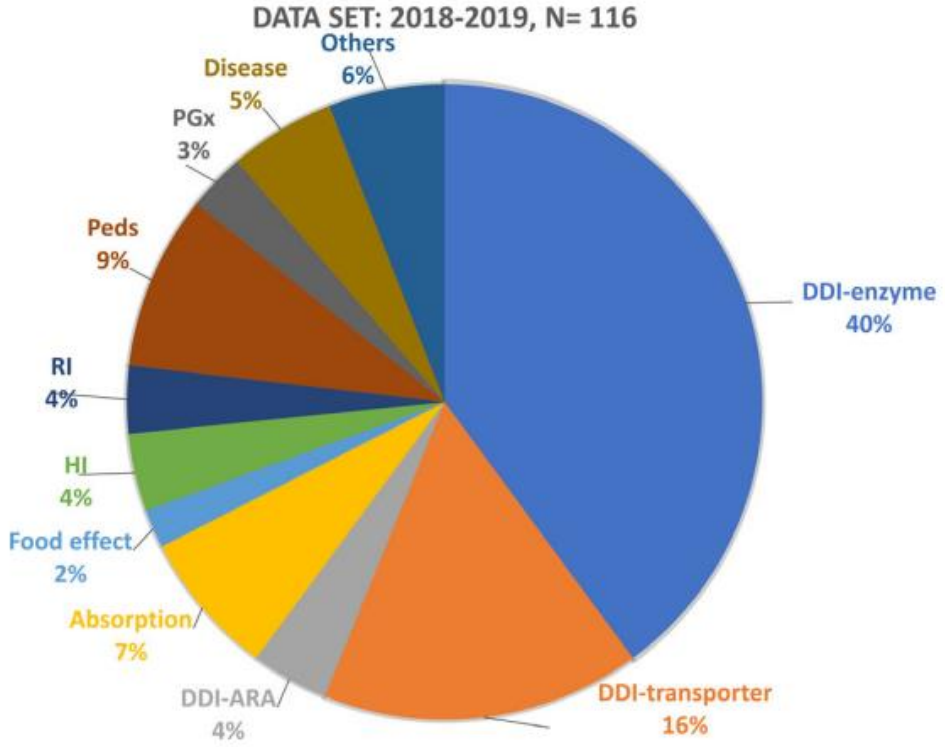
2

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

PBPK submissions 2018-19 56 INDs, 57 NDAs, 3 BLA
DDI models 39 adequate; 33 inadequate



Basis for adequacy of PBPK models for regulatory waivers and label

Drug is	Parameters	Verification
Precipitant – excluding CYP liability	Clearance	IV data or Pop PK
	Induction - Indmax	Indmax from in vitro experiment is calibrated against in vitro and in vivo rifampin Indmax
	Induction - EC50	From auto-induction in dose-dependent clinical PK data following repeated dosing of low clearance, sensitive substrate (ivosidenib)
	TDI – Ki, kinact	From auto-inhibition seen in time and dose dependence of clinical exposure of low clearance, sensitive substrate
	Reversible inhibition, Ki	Covered by 10-fold uncertainty analysis
	Fup for highly bound drugs	Covered by 2- to 3-fold uncertainty analysis
	Fu,mic	Covered by uncertainty analysis
Object of CYP inhibition	Clearance fm,CYP	• Low clearance drug for which gut metabolism is not important • Mass balance + in vitro (rCYPs or chemical inhibition) • DDI with strong inhibitor of the CYP isoform of interest
Object of OAT3 inhibition	fe, fT	• Mass balance (fe, fT) • DDI with strong precipitant

Basis for inadequacy of PBPK models for regulatory waivers & label

Population: Impact of disease on enzyme expression not understood

Drug as object of DDI

- CYP3A substrate with high clearance for which it is difficult to deconvolute gut metabolism, efflux and solubility etc. Model parameterisation and verification by top down approach is challenged by non-identifiability issues
- FmCYP values has not been validated with mass balance or DDI studies
- Uncertainty in model structure cannot be resolved (effects of CYP3A and P-gp are confounded)

Uncertainty in index substrate models: (model does not capture all reported DDI studies)

- Metformin (OCT2, MATE)
- Rosuvastatin (OATP1B1, BCRP)
- Digoxin model did not account for Pgp inhibition in kidney
- Fm,CYP uncertain in substrate drug model – e.g, bupropion

Drug as precipitant

CYP induction

- Lack of confidence in predicting time-dependent inhibition and induction directly using in vitro parameters (erdafitinib) - verification with clinical data difficult
- IVIVE for induction not well-established due to the complexity in this mechanism (EMA)

Efflux transporter inhibition (MATE1/2K, P-gp, BCRP)

- Difficult to resolve uncertainty in driving concentration and Ki with clinical data

Uptake transporter inhibition (OCT2, OATP1B1)

- Uncertainty in Ki

Limited experience – for example, in skin absorption

Many of tDDI PBPK submissions evaluate the effect of an investigational drug as a perpetrator

Evaluate the effect of an investigational drug on the PK of a transporter substrate with a well characterized pathway

Pathway	Drug as a substrate	Drug as a perpetrator
P-gp	rivaroxaban, ceritinib, prucalopride, upadacitinib, neratinib, naloxegol	ibrutinib, prucalopride, elagolix, fosnetupitant, ivosidenib, lasmiditan, erdafitinib, fedratinib, lefamulin
BCRP	prucalopride, upadacitinib	osimertinib, pexidartinib, fedratinib
OATP1B1/3	simeprevir, letermovir	fosnetupitant , ivosidenib, pexidartinib, fedratinib, lefamulin
OAT1/3	baricitinib	apalutamide, ivosidenib
OCT2/MATEs		prucalopride, apalutamide, pexidartinib, erdafitinib, fedratinib, lefamulin

Estimate the contribution from P-gp interaction to observed DDI for a P-gp/CYP3A dual substrate

Evaluate the role of transporters in ADME

Quantitative prediction

Support negative DDI prediction

In vitro Ki values tend to underpredict tDDI magnitude

A few examples:

Transporter	Substrate	Perpetrator	In vitro Ki (uM)	Ki fold-decrease	Reference
BCRP	Rosuvastatin	Osimertinib	2	10-20	Pilla Reddy, V. 2018 CPT:PSP
OCT2/OCT1	Metformin	Cimetidine	124/104	500	Burt, H.J. 2016 EJPS
OAT3	Pemetrexed	Ibuprofen	2.1	1	Posada MM. DMD (2015)
OAT3	Baricitinib	Probenecid	4.41 4.15 (pemetrexed)	1	Posada MM. CTS (2017)
OATP1B	Pravastatin	GDC-0810	0.15	100*	Chen Y. 2018 BDD

*combination of scaling and fu,inc

MSM or PBPK?

Advantages of dynamic PBPK models over static models

Advantage of dynamic PBPK over static models	However.....
Considers **dynamic**ally varying precipitant concentrations	Dynamic changes in [I] **not necessary** for predicting AUCR, a static measure of DDI
Complex DDI Parent and metabolite as precipitants Concurrent pathways for object of DDI • Multiple sites of DDI: Gut & liver for high CL CYP3A substrates • Multiple pathways; enzyme/transporter interplay Mixed mechanisms: inhibition and induction	Verification of individual contributions to DDI is challenged by **non-identifiability**. Therefore, considered area of low confidence
Allows estimation of **Cmax ratio** in addition to AUC ratio	AUC ratio generally represents a higher risk, except for intestinal or hepatic uptake when $AUC_{0\rightarrow t}$ is used
Incorporates sources of population **variability** arising from enzyme/ transporter polymorphism, demography, ethnicity and disease states	Variability from models are usually **over-estimated**
Extrapolation of DDI to untested populations after model is confirmed with DDI study in healthy, adult population	Changes in transporter/enzyme expression and physiology in the population of interest not known
Facilitates **'what-if' simulations of complex scenarios** • Study design: e.g., dosing regimens to ensure maximal interaction • Impact of dose staggering to minimize interactions	