
Physiology-based PK (PBPK) models for drug-drug interaction (DDI) trials and trials waiver

Kenichi Umehara, Yumi Cleary, Neil Parrott and Thierry Lavé

Pharmaceutical Sciences, Roche Pharmaceutical Research and Early Development (Basel, Switzerland)

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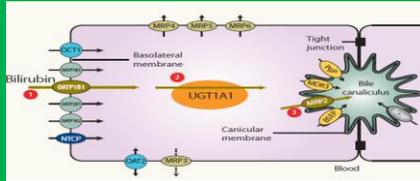
Aim at the presentation

- Background: why is PBPK modeling used for DDI risk assessment?
 - Supported by regulatory agencies
 - Scientific justification
- Guidance on the reporting PBPK modeling and simulations by EMA and FDA
- Case examples: support clinical trials and/or trials waiver
 - Perpetrator DDI via CYP enzymes
 - Victim DDI via CYP enzymes
 - Oral absorption DDI
- Potential further applications of PBPK modeling to other DDI areas
- Summary

Applications of PBPK modeling to clinical research

Model building → PK(PD) predictions in untested case scenarios

In vitro
(physicochemical, binding, enzyme, transporter parameters, etc.)



Animal and human PK(PD) (incl. e.g. human single and multiple ascending doses, food effect, drug-drug interaction (DDI) and mass balance)

Note: PBPK modeling supports anticipated human dose projection before Ph1

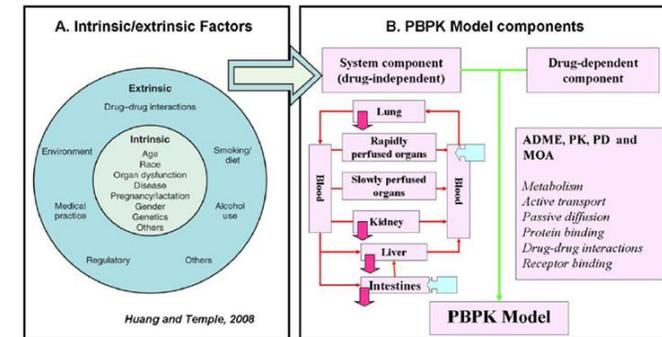
Establishment of PBPK models in HVs and/or patients

Application

Feedback

Predictions of PK(PD) and DDI profiles in untested case scenarios: among different populations and at different doses

- DDI (oral absorption / elimination)
- Organ impairment (hepatic / renal)
- Pediatrics

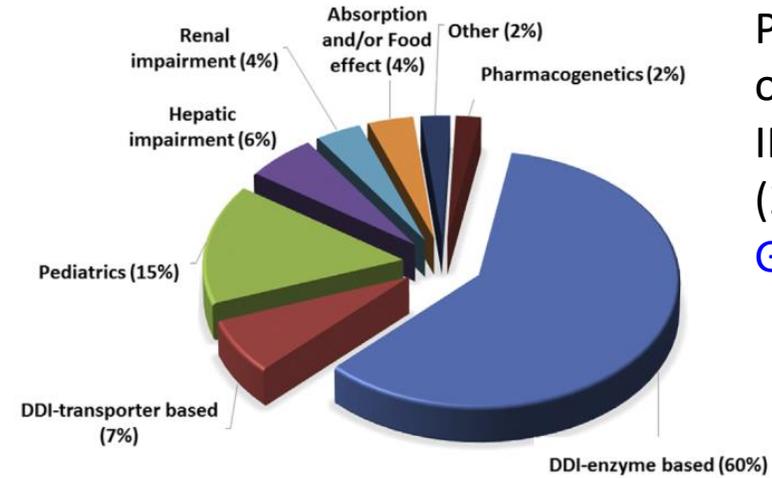
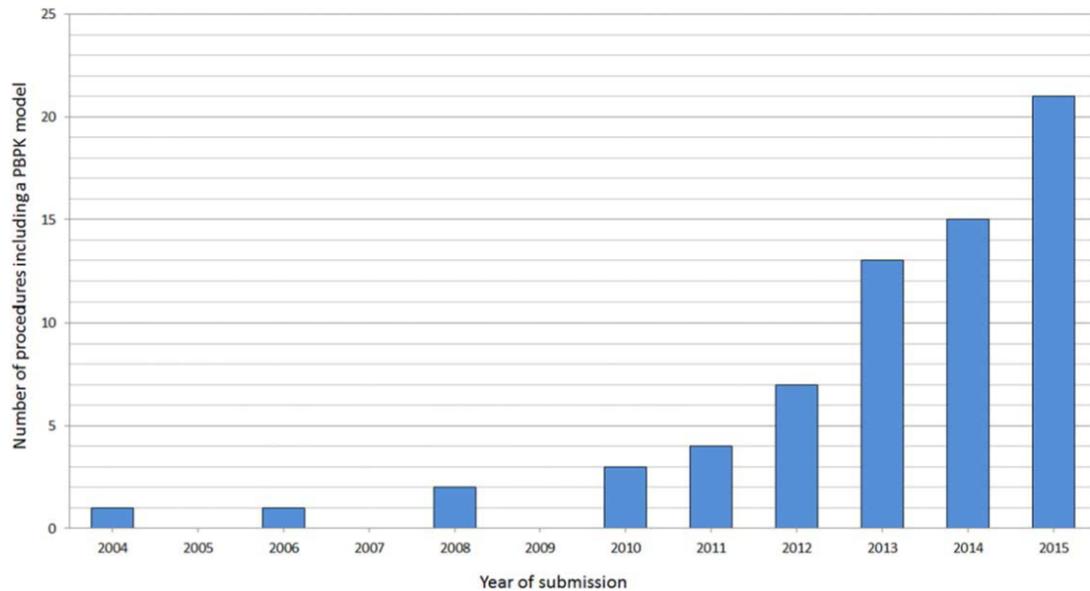


PBPK modeling: an established approach to impact on regulatory decisions

PBPK modeling is most frequently applied for DDI evaluation

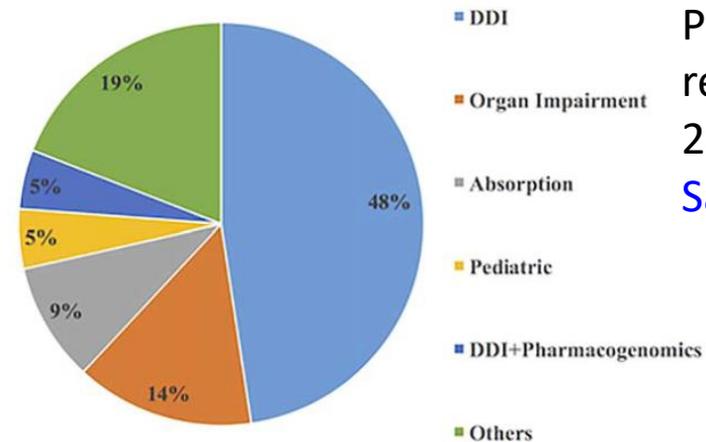
Submissions of procedures including PBPK models to **EMA** (2004-2015)

Luzon et al., 2017



PBPK modeling and areas of intended applications in IND/NDA reviewed by **FDA** (2008-2017, n=254)

Grimstein et al., 2019



PBPK application in NDA reviewed by **PMDA** (2014-2016, n=17)

Sato et al., 2017

Why is PBPK modeling frequently used for DDI risk assessment?

- Regulatory DDI guidance documents by [FDA \(2017\)](#) and [EMA \(2012\)](#)
 - (A) DDI risk assessment: static calculation (tier 1) → PBPK modeling (tier 2)
 - (B) A PBPK model-based framework
- (C) DDI potential evaluation methods have been well-established with mechanistic understanding the drug disposition and interaction properties (small molecules) - *Fit with the concept of PBPK modeling*

(A)

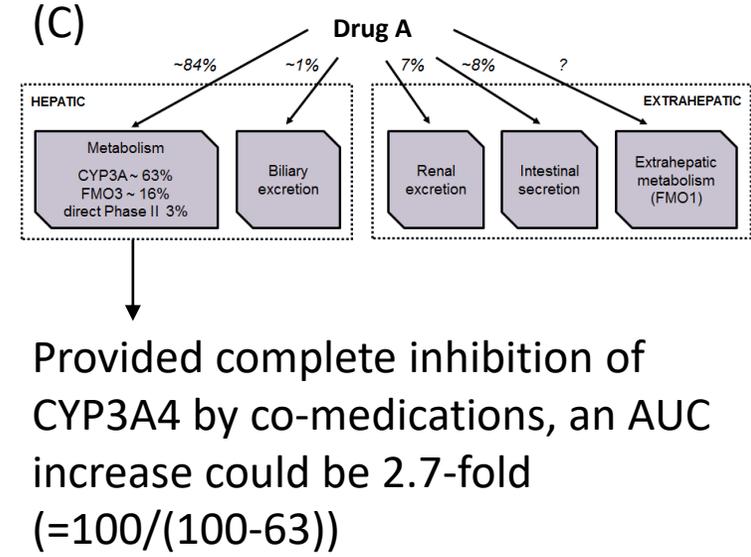
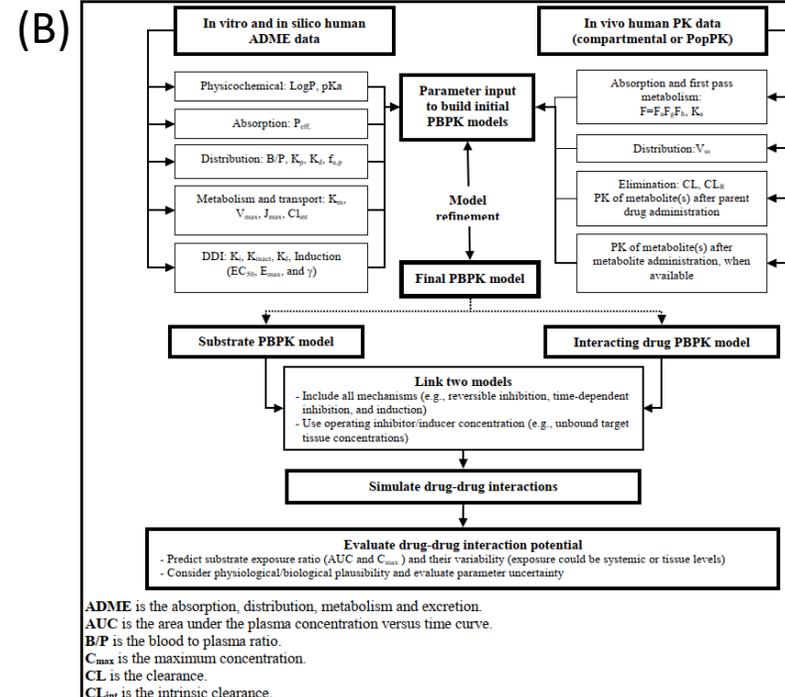
$$AUCR = \left(\frac{1}{[A_g \times B_g \times C_g] \times (1 - F_g) + F_g} \right) \times \left(\frac{1}{[A_h \times B_h \times C_h] \times f_m + (1 - f_m)} \right)$$

A is the effect of reversible inhibitions.
 B is the effect of TDI.
 C is the effect of induction.
 F_g is the fraction available after intestinal metabolism.
 f_m is the fraction of systemic clearance of the substrate mediated by the CYP enzyme that is subject to inhibition/induction.
 Subscripts 'h' denote liver.
 Subscripts 'g' denote gut.

Each value can be estimated with the following equations:

	Gut	Liver
Reversible inhibition	$A_g = \frac{1}{1 + \frac{[I]_g}{K_i}}$	$A_h = \frac{1}{1 + \frac{[I]_h}{K_i}}$
Time-dependent inhibition	$B_g = \frac{k_{deg,g}}{k_{deg,g} + \frac{[I]_g \times k_{inact}}{[I]_g + K_I}}$	$B_h = \frac{k_{deg,h}}{k_{deg,h} + \frac{[I]_h \times k_{inact}}{[I]_h + K_I}}$
Induction	$C_g = 1 + \frac{d \cdot E_{max} \cdot [I]_g}{[I]_g + EC_{50}}$	$C_h = 1 + \frac{d \cdot E_{max} \cdot [I]_h}{[I]_h + EC_{50}}$

[I]_h = f_{up} × (C_{max} + F₂ × k₁ × Dose / Q_h / R_b) (Ito, Iwatsubo, et al. 1998)
 [I]_g = F₁ × k₁ × Dose / Q_{em} (Rostami-Hodjegan and Tucker 2004)
 f_{up} is the unbound fraction in plasma. When it is difficult to measure accurately due to high protein binding (i.e., f_{up} < 0.01) in plasma, a value of 0.01 should be used for f_{up}.
 C_{max} is the maximal total (free and bound) inhibitor concentration in the plasma at steady state.
 F₁ is the fraction absorbed after oral administration; a value of 1 should be used when the data are not available.
 k₁ is the first order absorption rate constant in vivo; a value of 0.1 min⁻¹ (Ito, Iwatsubo, et al. 1998) can be used when the data are not available.
 Q_{em} is the blood flow through enterocytes (e.g., 18 L/hr/70 kg (Yang, Jamei, et al. 2007a)).
 Q_h is the hepatic blood flow (e.g., 97 L/hr/70 kg (Yang, Jamei, et al. 2007b)).
 R_b is the blood-to-plasma concentration ratio.



Regulatory perspectives

PBPK evaluation and reporting for DDI assessment

- Ultimate goal: waiving of clinical DDI trials by performing PBPK modeling
 - DDI prediction performance of an established model is to be reasonably verified
 - Otherwise, patients would not get the benefit from a newly approved drug in case of use of co-medications
- High regulatory impact analyses (EMA, 2019)
 - Use of PBPK model in place of clinical data
 - Victim DDI in a pharmacogenetic subpopulation
 - Complex DDIs where *e.g.* the combined effect of two inhibitors
 -
- Qualification of PBPK platform for the intended purpose
- Verification of models of compounds and interacting drugs
 - *In vitro*/pre-clinical data, clinical DDI and mass balance
 - Drug disposition diagram
 - Model building workflow
 - Identifiability of input parameters with uncertainties



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13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

[Guideline on the reporting of physiologically based pharmacokinetic \(PBPK\) modelling and simulation](#)

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	pharmacokinetics, modelling, simulation, qualification, predictive performance
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Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

Additional copies are available from:
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Question 1/2

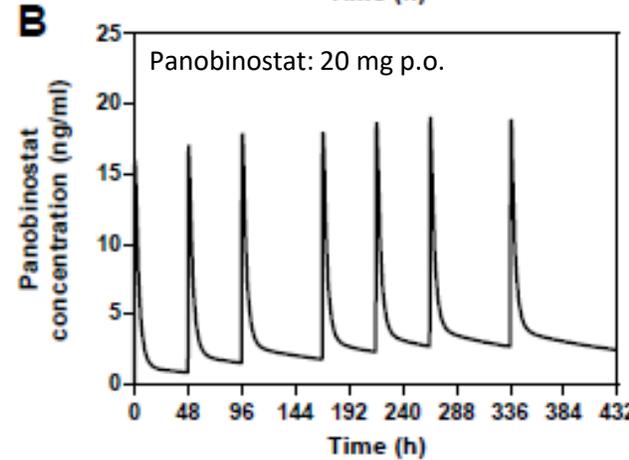
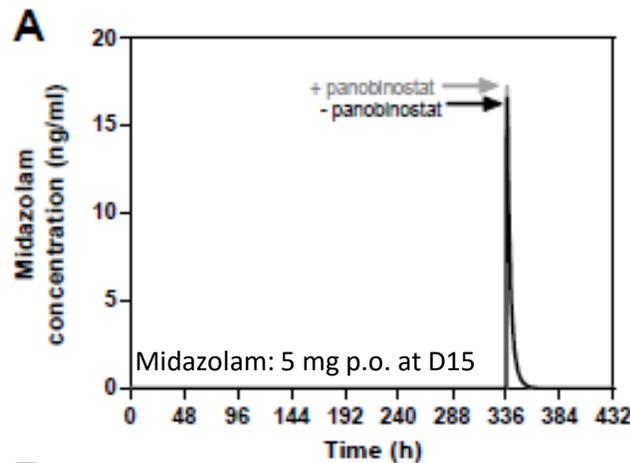
What can the following cases be predicted with PBPK modeling?

- a) Projection of anticipated human doses before Ph1
- b) Exposure change of the compound when a concomitant drug is administered
- c) Plasma concentration profiles in clinically untested case scenarios
- d) All above

Case example (1/7): reduction of clinical studies

Panobinostat: reversible and time-dependent inhibitor on CYP3A4

- PBPK modeling: a predicted AUC ratio of midazolam = 1.04
 - Static 'Net Effect Model': the predicted AUC ratio of midazolam = 1.95 (*i.e.* >1.25)
- No DDI trials



...Weak TDI *in vitro*, low dose/exposure, Monday/Wednesday/Friday dosing...

(Einolf *et al.*, 2017)

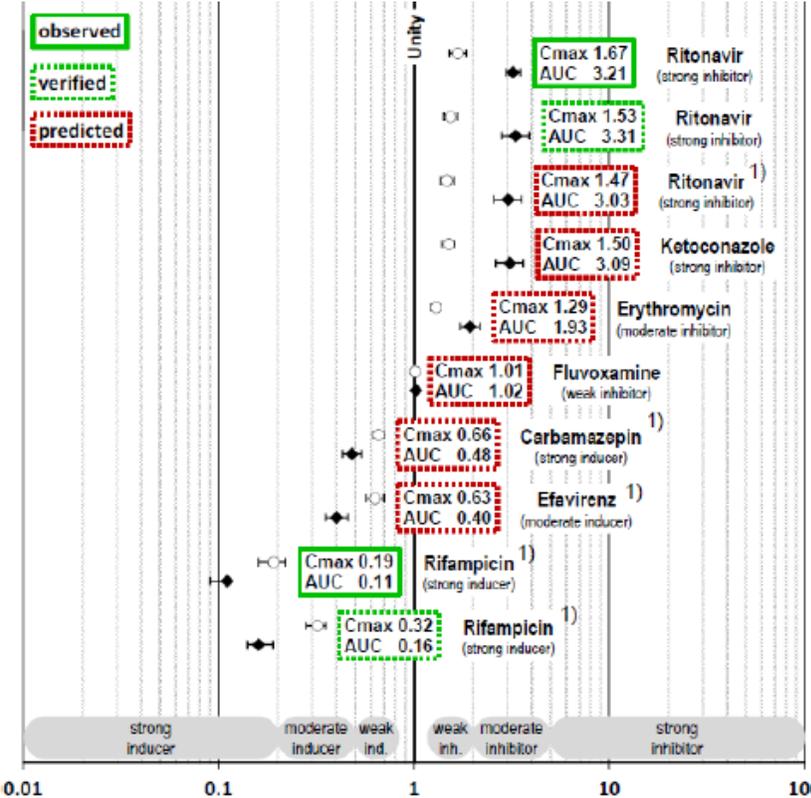
Impact on product label

CYP3A Substrates: Simulations using PBPK models predict that an exposure increase of less than 10% for the sensitive CYP3A substrate midazolam is likely following coadministration with panobinostat. The clinical implications of this finding are not known.

Case example (2/7): in place of clinical data

Ribociclib: a substrate as well as weak time-dependent inhibitor for CYP3A4

- PBPK modeling could show reduction of the number of DDI studies
- Extrapolation to the victim DDI potential prediction at steady-state (**untested case scenario**) for dose adjustment with concomitant use of CYP3A4 perpetrators (600 mg → 400 mg)



Unnecessary clinical DDI risk evaluation

1) Ribociclib dose for simulations: 600 mg; otherwise 400 mg was used. [Kisqali® Clinical Pharmacology Review \(FDA, 109092Orig1s000\)](#)

Case example (3/7): model verification of interacting drugs

Ritonavir: a strong (time-dependent) CYP3A inhibitor

- Ribociclib: a fraction metabolized by CYP3A4 (fm,CYP3A4) could not be confirmed by the *in vitro* assay
 - The ribociclib – ritonavir DDI study was conducted
 - To recover the clinical findings, verification of a ritonavir PBPK model was additionally investigated

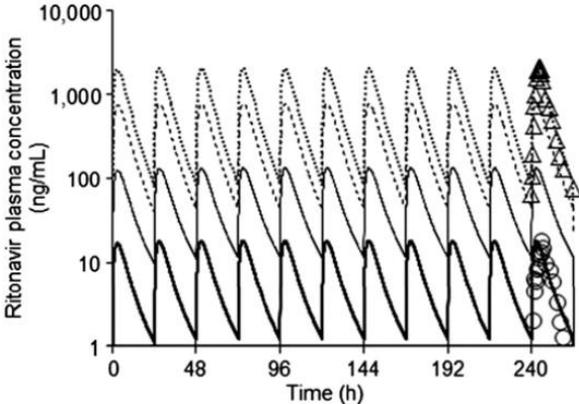


FIGURE 1 Plasma concentration profiles of ritonavir over time after multiple oral administration. Lines give the predicted PK profiles of ritonavir (thick solid: 20 mg; thin solid: 50 mg; broken: 100 mg; and dotted: 200 mg p.o., q.d., n = 10). Open circles and triangles show plasma concentrations as measured at day 11 over multiple oral administration of ritonavir at 20 mg and 200 mg, respectively (n = 10–11) (Mathias et al., 2009)

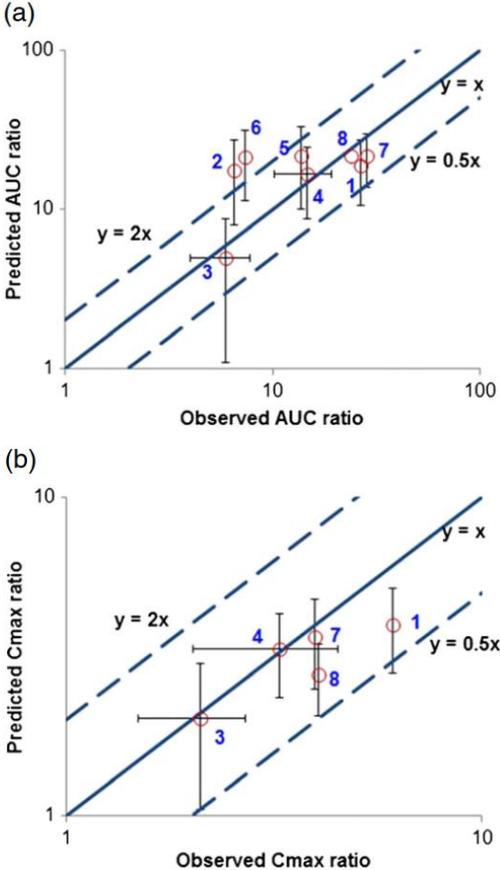


FIGURE 4 Predicted AUC and C_{max} ratios of midazolam with and without ritonavir in comparison to the respective clinical observations. Predicted (a) $AUC_{(0-t)}$ ratios or AUC_{inf} ratios, and (b) C_{max} ratios of midazolam in the presence and absence of ritonavir were compared to the respective clinical study data (1: Ancrenaz et al. (2013); 2: Eichbaum et al. (2013); 3 and 4: leiri et al. (2013); 5: Knox et al. (2008); 6: Morcos et al. (2013); 7: Greenblatt et al. (2009); 8: Mathias et al. (2010)). Observed AUC ratios of midazolam in Eichbaum et al. (2013) and Morcos et al. (2013) were calculated using partial $AUC_{(2-4h)}$, and using apparent clearance values of midazolam (control: 28.5 ml/min/kg, inhibited: 2.1 ml/min/kg), respectively. All data expressed as mean ratios with SD (if any) are plotted in logarithmic x and y axes. Broken and solid lines represents $y = 2x$, $y = 0.5x$ and $y = x$, respectively

(Umehara et al., 2018)

Case example (4/7): two-dimensional approach to estimate $f_m, CYP3A4$

Alectinib: a CYP3A4 substrate in vitro

- Two-dimensional analysis
 - F_g and $f_m, CYP3A4$ of alectinib could be identified to recover the AUC and C_{max} ratios observed in the posaconazole (400 mg b.i.d.) DDI study
 - Observed AUCR = 1.60 and $C_{max} R=1.25$ at 40 mg alectinib

(Cleary and Gertz *et al.*, 2017)

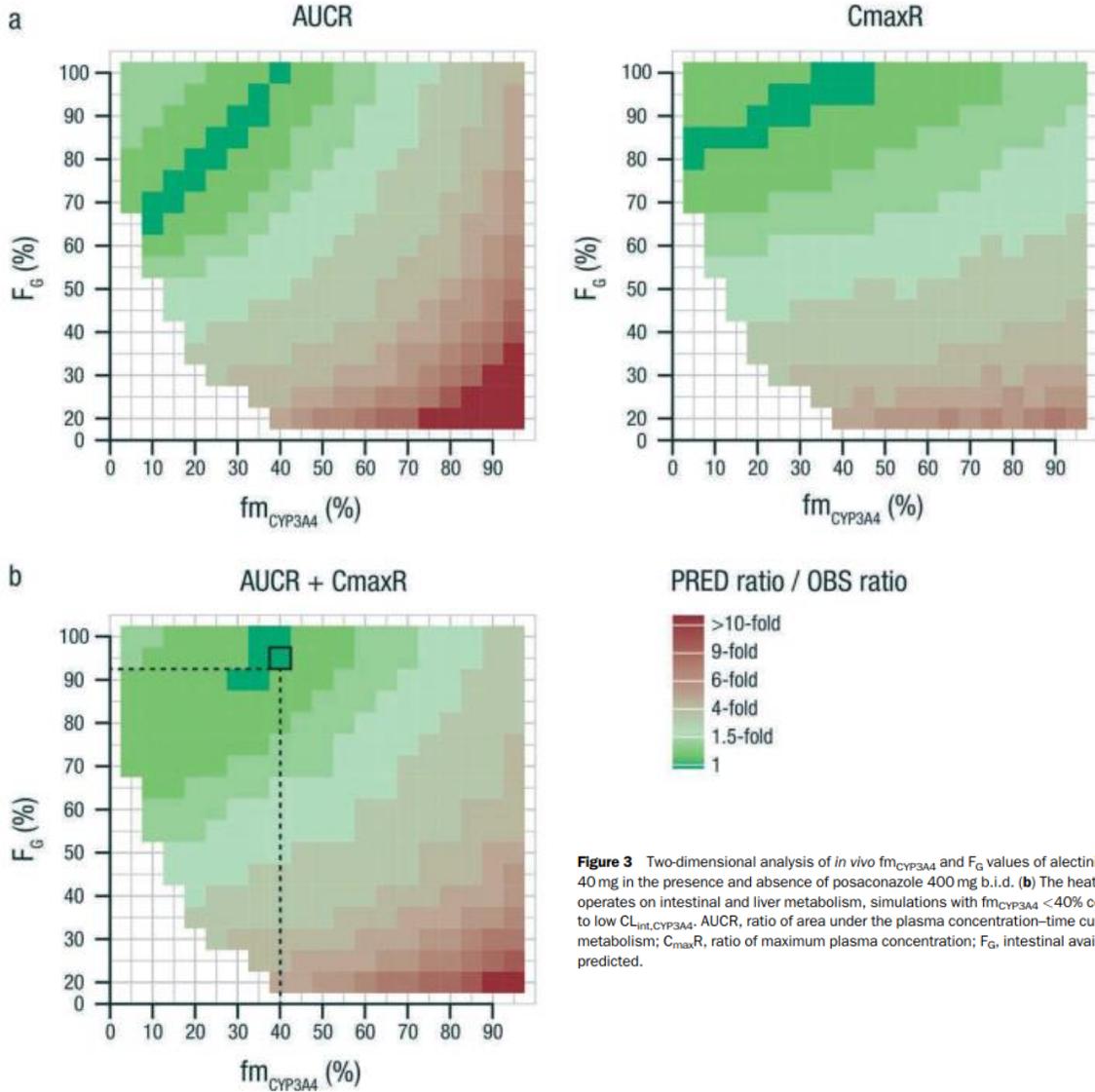


Figure 3 Two-dimensional analysis of *in vivo* $f_{m,CYP3A4}$ and F_g values of alectinib. (a) The ratios of predicted to observed AUCR and $C_{max}R$ of alectinib 40 mg in the presence and absence of posaconazole 400 mg b.i.d. (b) The heat maps of the combined scores of AUCR and $C_{max}R$. As intrinsic clearance operates on intestinal and liver metabolism, simulations with $f_{m,CYP3A4} < 40\%$ could not achieve sufficient intestinal metabolism to reach F_g of ≤ 0.7 due to low $CL_{int,CYP3A4}$. AUCR, ratio of area under the plasma concentration–time curve; b.i.d., twice daily; $CL_{int,CYP3A4}$, intrinsic clearance through CYP3A4 metabolism; $C_{max}R$, ratio of maximum plasma concentration; F_g , intestinal availability; $f_{m,CYP3A4}$, metabolic fraction by CYP3A4; OBS, observed; PRED, predicted.

Case example (5/7): PK and victim DDI in a pharmacogenetic subpopulation

Siponimod: a sensitive CYP2C9 substrate

- Prediction of the impact of CYP2C9 genotypes on the PK and DDI potential
 - PBPK modeling is a powerful tool to estimate the PK in CYP genotypes with significantly less frequencies (as 0.003 for CYP2C9*3*3) – *highly likely being untested case scenario*

Table 1 Intrinsic clearance of allelic CYP2C9 genotypes relative to wild-type genotype (CYP2C9*1/*1) for SimCYP model construction

CYP2C9 genotype	In vitro PG ratios ^a	CL _{int} (μL/min/pmol) ^b
CYP2C9*1/*1	1.0 ± 0.062	49.07 ± 3.04
CYP2C9*1/*2	0.673	33.03
CYP2C9*1/*3	0.5445	26.72
CYP2C9*2/*2	0.345 ± 0.006	16.93 ± 0.29
CYP2C9*2/*3	0.217	10.65
CYP2C9*3/*3	0.089 ± 0.023	4.37 ± 1.14

Student's *t* tests are applied for comparing the significant difference of CYP2C9*1/*1 to CYP2C9*2/*2 (*p* value 0.0477) and CYP2C9*1/*1 to CYP2C9*3/*3 (*p* value 0.0424), respectively

CYP cytochrome P450, PG pharmacogenetics

^aThe in vitro PG ratio data is from human liver microsomes

^bThe intrinsic clearance in the different genotypes was estimated by multiplying the in vitro PG ratio with the intrinsic clearance in the wild-type genotype (49.07 μL/min/pmol) simulated from the SimCYP (V12) retrograde model

(Jin *et al.*, 2017)

Table 4 Predicted contribution ratio of CYP2C9 and other P-450 enzymes for siponimod human metabolism

Genotype	Predicted enzyme contribution ratio (% fm)				
	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP3A4
CYP2C9*1/*1	0.24	1.54	80.84	0.15	17.23
CYP2C9*1/*2	0.47	2.54	68.83	0.23	27.94
CYP2C9*1/*3	0.49	3.36	62.53	0.30	33.32
CYP2C9*2/*2	0.60	3.48	57.81	0.33	37.78
CYP2C9*2/*3	0.83	4.81	43.84	0.43	50.09
CYP2C9*3/*3	1.28	7.74	11.31	0.76	78.91

CYP cytochrome P450, fm fraction metabolised

CYP2C9 genotype dependent CL_{int} and fm estimations based on *in vitro*:

pop-PK analysis would refine the data as input for PBPK modeling

PK simulation

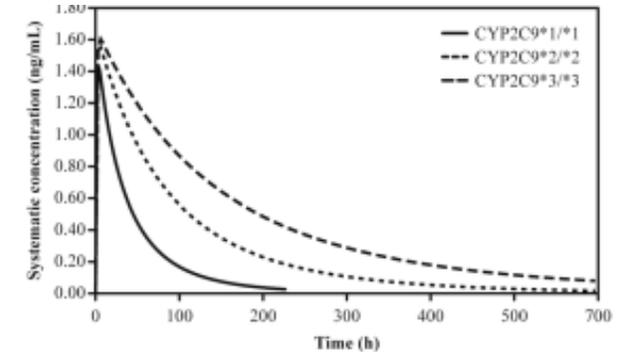


Fig. 7 Simulated mean plasma concentration of siponimod after single oral dose of 0.25 mg in the genetic polymorphic population of homozygote CYP2C9 genotypes using SimCYP version 12. Only simulated profiles of the three homozygotes genotypes are shown. CYP cytochrome P450, h hours

DDI evaluation

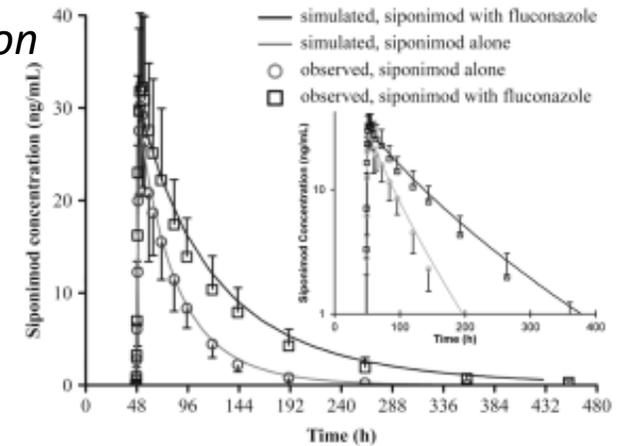
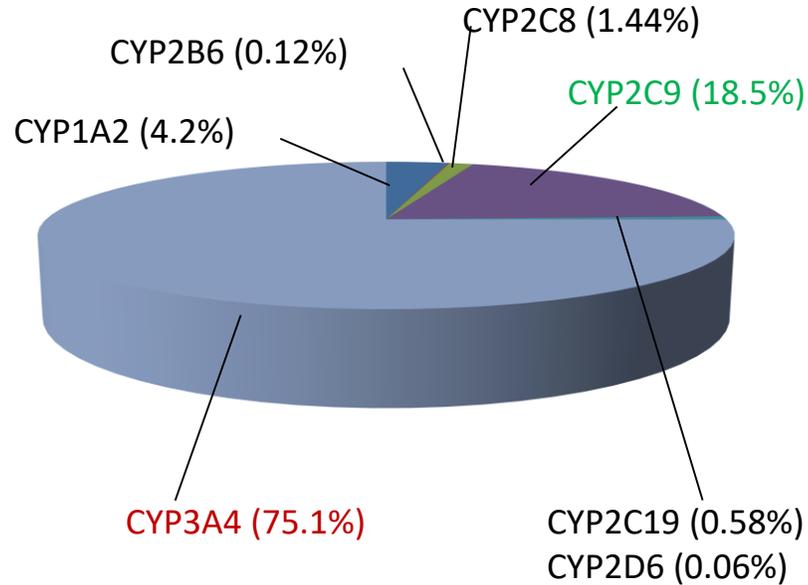


Fig. 6 Predicted siponimod mean plasma concentration in the absence and presence of fluconazole (200 mg) inhibition (dose regimen iv, SimCYP version 16). Observed data (*n* = 14 for siponimod alone; *n* = 11 for siponimod with fluconazole) are included for comparison. The SimCYP simulation was performed in 110 virtual subjects. h hours

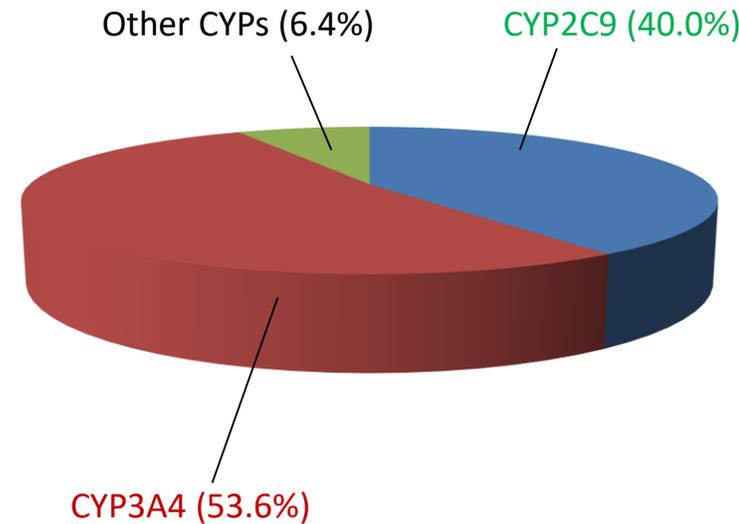
Case example (6/7): complex DDIs

Ruxolitinib: a dual substrate of CYP3A4 and CYP2C9

(A) *In vitro* CYP phenotyping



(B) *In vivo* ketoconazole (200 mg b.i.d.) DDI study (observed AUCR = 1.91 at 10 mg ruxolitinib)



Untested case scenario: the dual inhibition effect of fluconazole on CYP3A4 and CYP2C9

Fluconazole: Simulations using **physiologically-based pharmacokinetic (PBPK) models** suggested that fluconazole (a dual CYP3A4 and CYP2C9 inhibitor) increases steady state ruxolitinib AUC by approximately 100% to 300% following concomitant administration of 10 mg of Jakafi twice daily with 100 mg to 400 mg of fluconazole once daily, respectively [see *Dosage and Administration (2.3)* and *Drug Interactions (7.1)*].

(Umehara et al., 2019, in press)

Case example (7/7): absorption DDI modeling

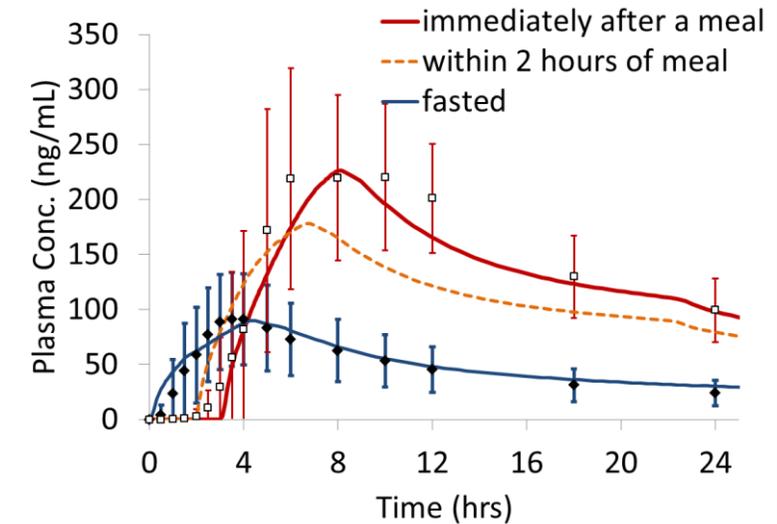
Support for the Filing of Alectinib

Impact:

- Support for lack of interaction with gastric acid reducing co-medications – no need for further clinical studies
- Support for impact of time of dosing with a meal – no need for further clinical studies
- Delivered understanding of exposure vs dose relationship guided dose and dose regimen selection and supported market formulation selection

Highlights:

- Prediction of DDI with PPIs confirmed strengthening case for no interaction
- Convincing simulation of food effect to be used in label
- Predicted effect of SLS in formulation confirmed and verified model used to support selection of market formulation



Current status & Next steps:

- **A convincing model integrating in vitro and clinical data has been constructed**
- **Documentation and model files were mentioned in FDA review of NDA filing**
- **Roche/Chugai paper AAPS Journal July 2016**
- **Model applied for further formulation development in collaboration with Chugai**

(Parrott et al., 2016)

Question 2/2

Drug A is eliminated by hepatic CYP3A4. What is a «clinically untested case scenario» which can be predicted? The PBPK model of drug A is verified as a CYP3A4 substrate using PK data in healthy adults.

- a) PK change at fed state
- b) Inhibition effects of drug A on the PK of CYP2C9 substrates
- c) Dose adjustment of drug A when a CYP3A4 inhibitor is co-administered
- d) Dose adjustment of drug A in infants
- e) PK differences in healthy volunteers and target disease populations

PBPK-DDI modeling: current achievements and expected applications

- **Achievements**

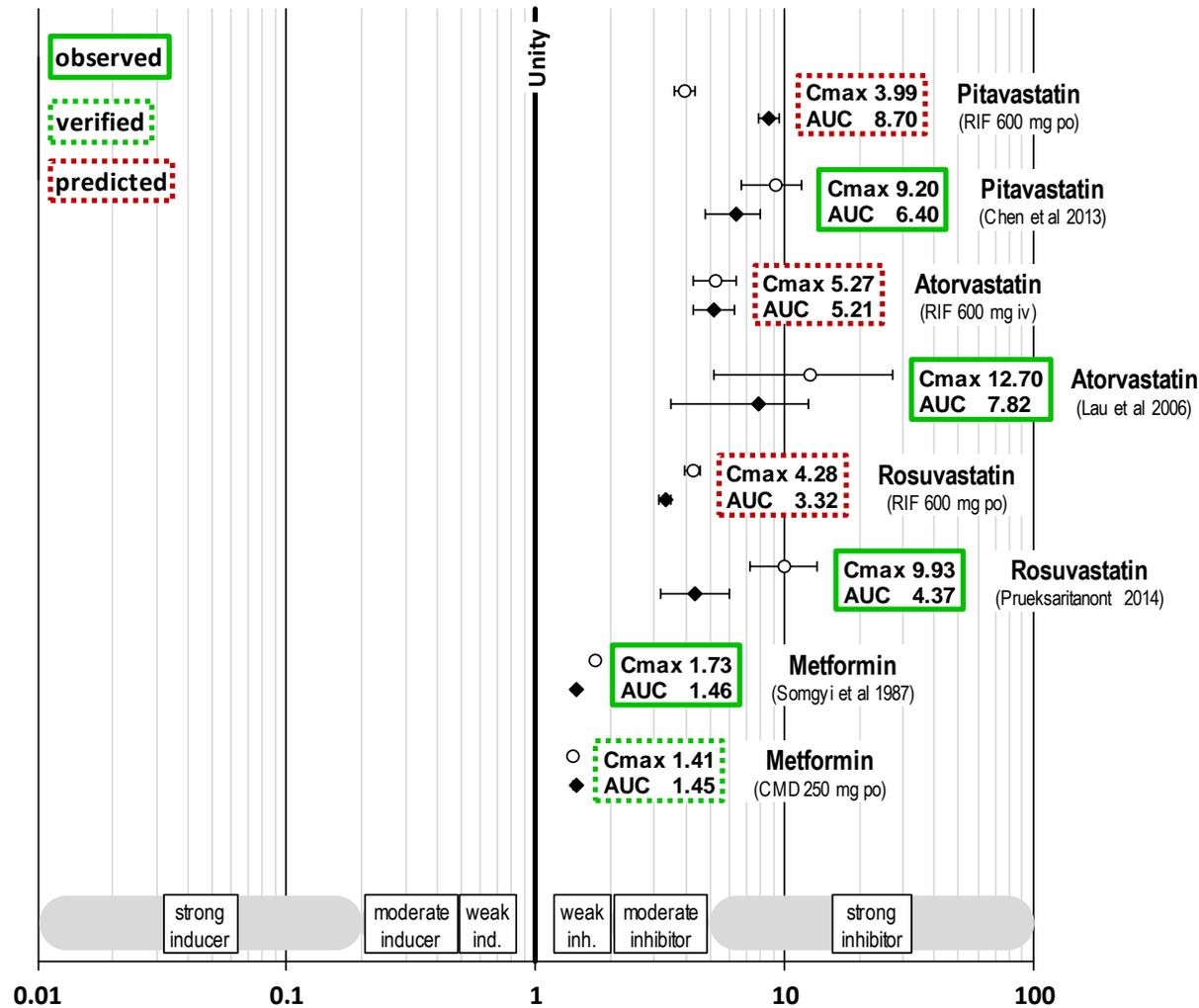
- Waiving of unnecessary (untested) PK / DDI studies
 - Victim DDI via major CYP enzymes
 - Perpetrator DDI *e.g.* time-dependent inhibition (and induction)
 - Absorption DDI with acid-reducing agents
- Dose adjustment with *e.g.* co-medications (incl. prediction of PK variability)
- Support clinical DDI study designs

- **Expected applications**

- Complex DDI of a drug showing time-dependent inhibition and induction on CYP enzymes
- DDI via non-CYP enzymes (*e.g.* UGTs)
- Transporter DDI
- DDI among target patients/populations

Transporter DDI prediction

Partial verification of model performance for transporter DDI via OATP1B1 and OCT2/MATEs



Model limitations:

- DDIs on statins
 - Under-estimation of C_{max} ratio by 2-fold to 3-fold due to lack of mechanistic V_h (mainly governing V_{ss}) change by strong OATP1B1 inhibition (likely not the case of weak OATP1B1 inhibition)
 - Intestinal DDI via P-gp (atorvastatin) and BCRP (rosuvastatin): no verification due to lack of numbers of the reference clinical data
- DDIs on metformin
 - The current value OCT2 K_i (0.25 μM) of cimetidine, which is approximately 500-fold lower than the *in vitro* K_i value in transfected HEK cells, reflects the inability of the current model to recover the indirect effect of MATE transporter inhibition of cimetidine on the activity of OCT2 (Burt et al., 2016).

Pitavastatin, atorvastatin, rosuvastatin and metformin were orally administered at 4 mg (single dose), 40 mg (single dose), 5 mg (single dose) and 250 mg (once daily), respectively, after co-medication of rifampicin RIF (600 mg i.v. or p.o., single dose for statins) and cimetidine CMD (400 mg p.o., twice daily for metformin). Predicted AUC (inf or tau) and C_{max} ratios of victim drugs were expressed as geometric mean with 90% confidence interval (n = 12 or 50).

Summary: take home messages

- An application of PBPK modeling for supporting the clinical DDI trials is most frequently considered among the areas of the intended use in submission dossiers reviewed by regulatory agencies
 - A concept of DDI risk assessment has been well-established
 - Strongly supported by regulatory DDI guidance documents ([FDA, 2017](#); [EMA, 2012](#))
- Conducting PBPK modeling for untested case scenarios potentially results in waiving of clinical DDI trials
 - Benefit-risk decisions should be made for patients to avoid unexpected adverse events by exposure increase / decrease of drugs by co-medications: categorization of high regulatory impact analyses ([EMA, 2019](#))
 - Dose adjustment with *e.g.* co-medications (incl. prediction of PK variability)
 - Prerequisite: Qualification of the software and scientific verification of models of compounds and interacting drugs
 - Guidance on the reporting PBPK modeling and simulations by [EMA \(2019\)](#) and [FDA \(2018\)](#)
- Case examples: CYP-based and oral absorption DDI
 - Note: population PK analyses will support PBPK model verification (*e.g.* CL among pharmacogenetic populations, absorption rate constant k_a)
- Applications of PBPK modeling to other DDI areas (as via transporter) are highly expected while there are several scientific limitations for the moment

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***Doing now what patients need
next***