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Role of physiologically based pharmacokinetics (PBPK) in regulatory submissions

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Disclaimer

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Outline of the Presentation

- EMA reporting of PBPK Guideline
- What a regulatory assessor always looks for in PBPK models
- Regulatory experiences using PBPK in Europe (EMA)

Use of PBPK in Regulatory Submissions

Table 5 Purpose of PBPK models submitted to EMA in finalized and ongoing procedures up to 31 December 2015[a]

Main categories	Specific purpose		Number
Intrinsic factors	General description of PK parameters		8
	Organ impairment (hepatic and/or renal)		8
	Effect of polymorphisms		7
	Effect of ethnicity		4
	Differences across disease states (hepatitis C virus infected patients)		2
	Differences across age groups		1
Extrinsic factors (interactions)	DDI involving enzymes	drug as victim	37
		drug as perpetrator	23
	DDI involving transporters	drug as victim	3
		drug as perpetrator	8
	DDI based on gastric pH changes		2
	Food-drug interactions		2
	Interaction with cigarette smoke		1
Drug parameters	Comparison between strengths/formulations		8

DDI, drug-drug interactions; EMA, European Medicines Agency; PBPK, Physiologically Based Pharmacokinetic; PK, pharmacokinetics.
[a]Note: A given model may have been submitted with more than one intended purpose and/or more than one model may have been submitted within the same procedure.

PBPK in EMA Regulatory Guidelines

- **Investigation of Drug interactions, 2012**

  *"The **PBPK model needs to be qualified for its purpose**. In general, the performance of the model needs to be supported by relevant in vivo data."…"**sensitivity analysis**".*

- **Pharmacogenetic methodologies in PK evaluation of medicinal products, 2012**

  "*In silico PBPK modelling….may be helpful when optimising the design of in vivo PK studies*" *.."**PBPK model needs to be qualified**…"…" performance of the model needs to be supported by relevant in vivo data"*

- **PK evaluation of modified release dosage forms, 2014**

  …"IVIVC modelling…..**PBPK** models"

- **Reflection paper, Extrapolation in development of medicines for paediatrics, 2017**

  …"*modelling and simulation approaches (e.g. population PK, **PBPK**) incorporating knowledge of growth and maturation effects on PK are recommended to strengthen conclusions drawn from often sparse observed PK data*."

- **December 2018: Reporting of PBPK modelling**

Guideline on the reporting of PBPK modelling and simulation

EMA/CHMP/458101/2016

Understand how changes in key input parameters affect the model output

To certify that a PBPK platform can be used for an intended regulatory purpose

To certify that the drug model can predict the observed PK of the compound before the model can be used for simulations of special situations

Regulatory Impact

The extent of qualification required depends on the regulatory impact.

High impact: instead of clinical data, leading to a warning (or lack thereof) in the label

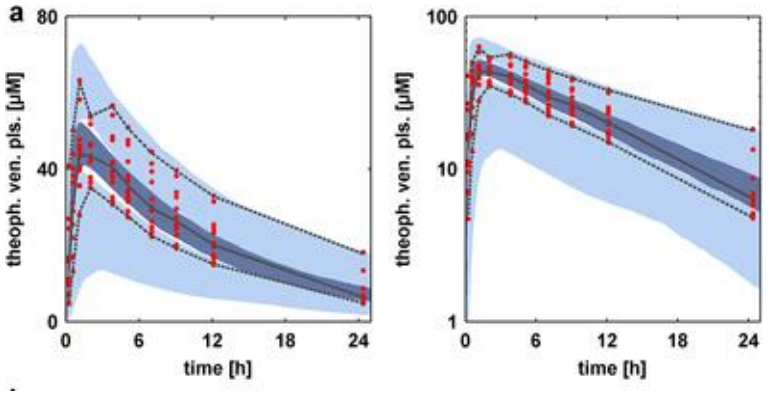
Medium and low impact: when confirmatory clinical data is available

Qualification of the Platform (Software)

- To certify that a platform can be used for an intended regulatory purpose
- Is the platform able to perform that specific type of simulation?
- Is the software able to correctly simulate a similar scenario with other drug substances?
- Literature data may be acceptable (for the same version of a platform)

Evaluation of the Predictive Performance

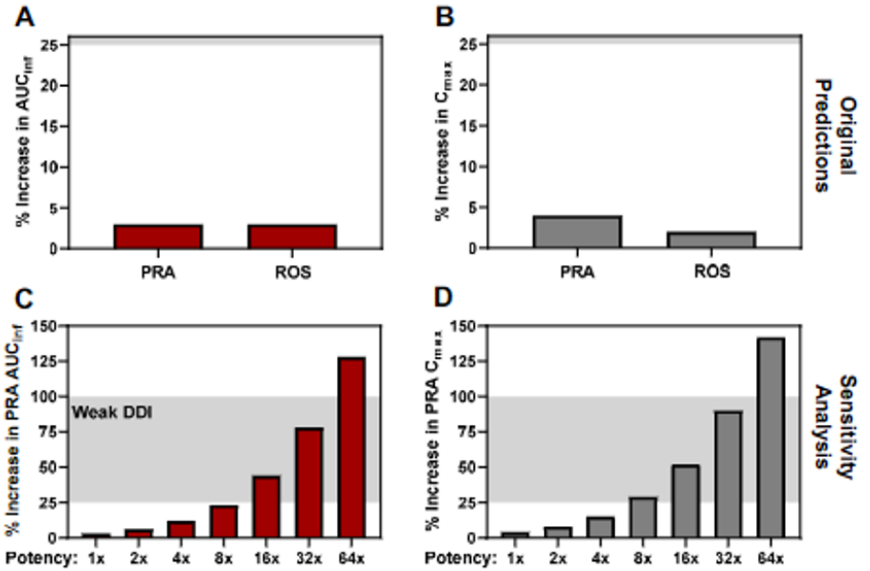
- Can the model predict the range of observed outcome from *in vivo* PK studies or pop-PK analyses
- Comparison of simulated and observed data
- When used for simulations in a new population, simulation of the observed exposure in other populations should be included



Sensitivity Analysis

Understanding of how quantitative changes in key model input parameters can influence the model output

Parameters, their ranges and values should be justified



What a Regulatory Assessor Always Looks for

Credibility Matrix

- Question of interest
- Regulatory impact
- Platform qualification
- Precision level
- Risk based analysis of decision consequence
- Model informed decision

Selected Regulatory Cases

Small molecules

- CYP3A4 victim interaction
- PgP victim interaction

Biologics

- IL-6 mediated DDI
- Paediatric extrapolation

Further examples

- CYP2D6 polymorphism
  - Eliglustat (Cerdelga) – numerous recommendations for different CYP2D6 phenotypes and CYP inhibitor or organ impairment combinations
- UGT1A1 victim
  - Binimetinib (Mektovi) – SmPC text 4.5 “Therefore, the extent of drug interactions mediated by UGT1A1 is minimal, and unlikely clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 inducers or inhibitors should be administered with caution.”
  - Olaparib (Lynparza) – SmPC text 5.2 “PBPK simulations suggest this is not of clinical importance”
- Hepatic impairment
  - Encorafenib (Braftovi) – SmPC text 5.2 “As encorafenib is primarily metabolised and eliminated via the liver, based on PBPK modelling, patients with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4).”
- Renal impairment
  - Regorafenib (Stivarga) – SmPC text 5.2 “Available clinical data and physiology-based pharmacokinetic modelling indicate similar steady-state exposure of regorafenib and its metabolites M-2 and M-5 in patients with mild or moderate renal impairment, compared to patients with normal renal function. In patients with severe renal impairment compared to patients with normal renal function, regorafenib exposure was similar while exposure to M-2 and M-5 was decreased by about 30% under steady-state conditions, which is not considered clinically relevant. The pharmacokinetics of regorafenib has not been studied in patients with end-stage renal disease. However, physiology-based pharmacokinetic modelling does not predict any relevant change in exposure in these patients.”

Further examples

- Gastric emptying
  - Dulaglutide (Trulicity) SmPC text 4.5 “For the 4.5 mg dose, absence of major clinically relevant interactions was predicted by physiologically-based pharmacokinetic (PBPK) modelling simulations.”
- Physiologically based biopharmaceutic modelling (PBBM)
  - Support in vitro dissolution specifications (IVIVC level A)
  - Change of manufacturing site (waive bioequivalence study)
- Antibody drug conjugate
  - Polatuzumab Vedotin (Polivy) – SmPC text 4.5 “Based on physiological-based pharmacokinetic (PBPK) model simulations of MMAE released from polatuzumab vedotin, strong CYP3A4 and P-gp inhibitors (e.g., ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE by 48%. Caution is advised in case of concomitant treatment with CYP3A4 inhibitor. Patients receiving concomitant strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities. Unconjugated MMAE is not predicted to alter the AUC of concomitant medicines that are CYP3A4 substrates (e.g., midazolam).”

Fedratinib (Inrebic)

CYP3A4 victim interaction

JAK2 inhibitor 400mg QD, upper limit of the therapeutic margin of fedratinib of 1.25

Excretion 77% in faeces, 5% in urine, majority unchanged and 19 minor metabolites

Mostly metabolised by CYP3A4 & 2C19

DDI aspects of interest:

- auto-inhibition
- time-dependent inhibition
- mixed inhibition/induction of CYP enzymes including CYP3A

Scope of PBPK:

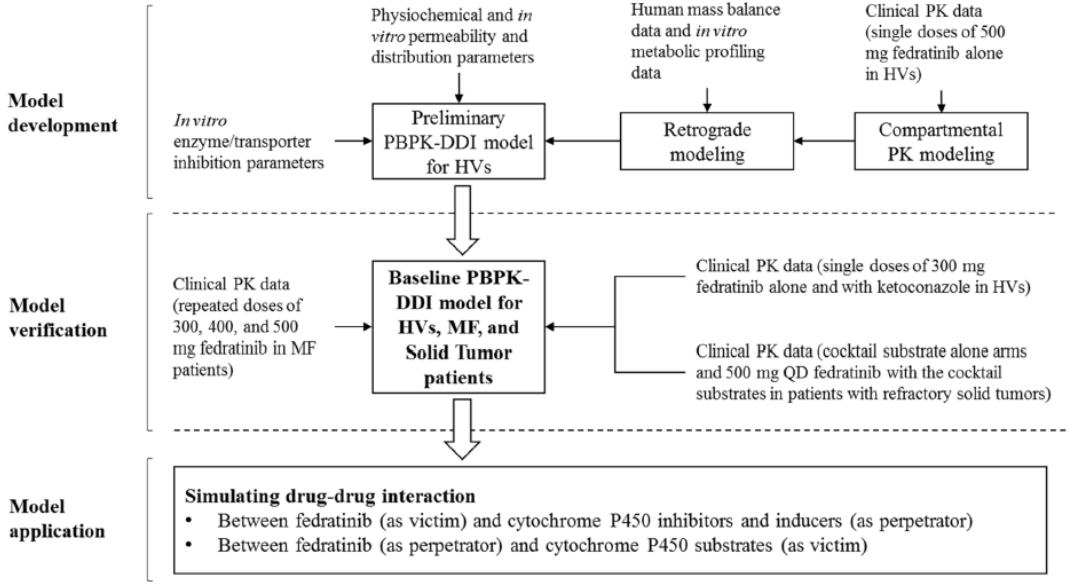
- CYP-fedratinib (victim or perpetrator)
- transporters (perpetrator)
- moderate to high regulatory impact

Fedratinib (Inrebic)

Data input

Clinical PK data included in the model

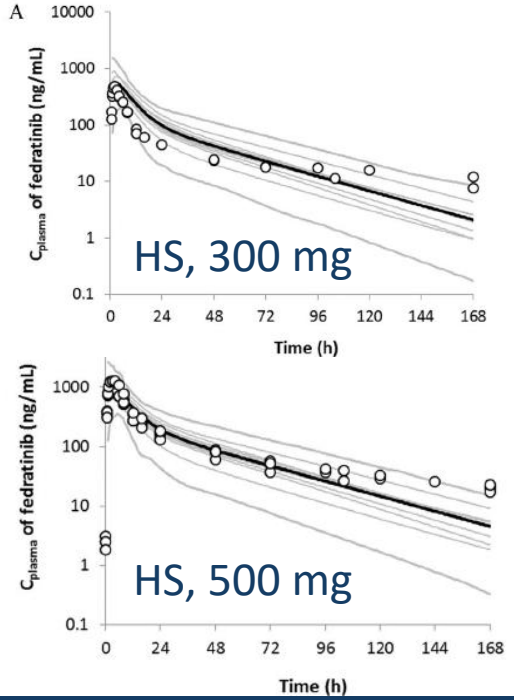
- Repeated doses of fedratinib in patients with myelofibrosis (MF)
- DDI fedratinib (victim) and ketoconazole in healthy subjects
- DDI fedratinib (perpetrator) and cocktail of midazolam, omeprazole and metoprolol in patients with refractory solid tumours

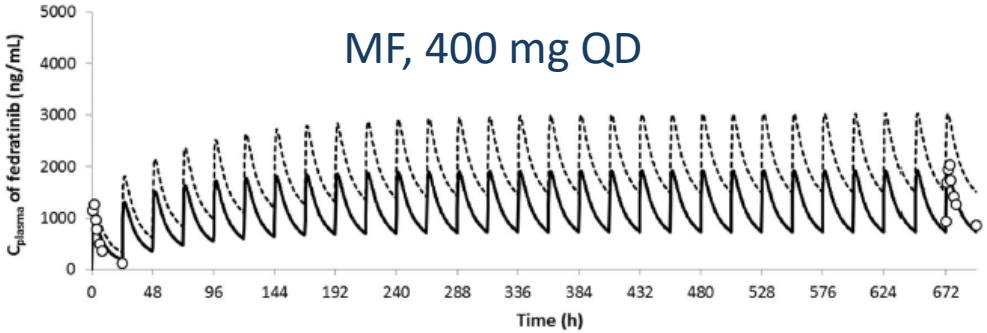


EPAR, illustration from Wu et al, Cancer Chemotherapy & Pharmacology, 2020

Fedratinib (Inrebic)

Evaluation of the predictive performance



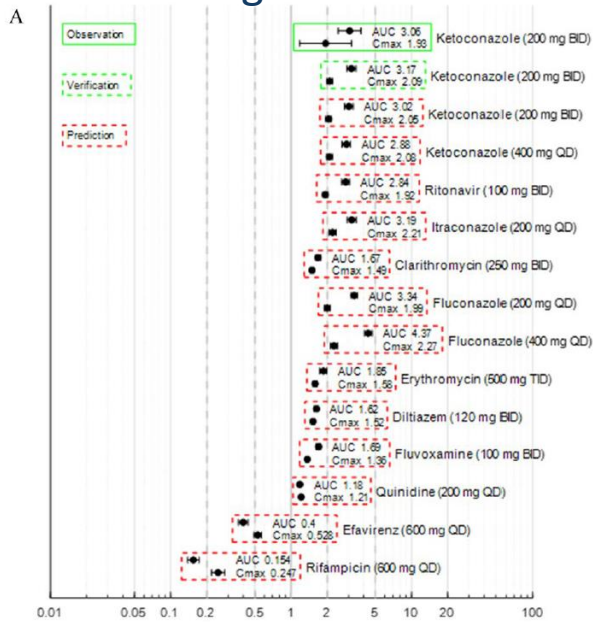


Data from Wu et al, Cancer Chemotherapy & Pharmacology, 2020

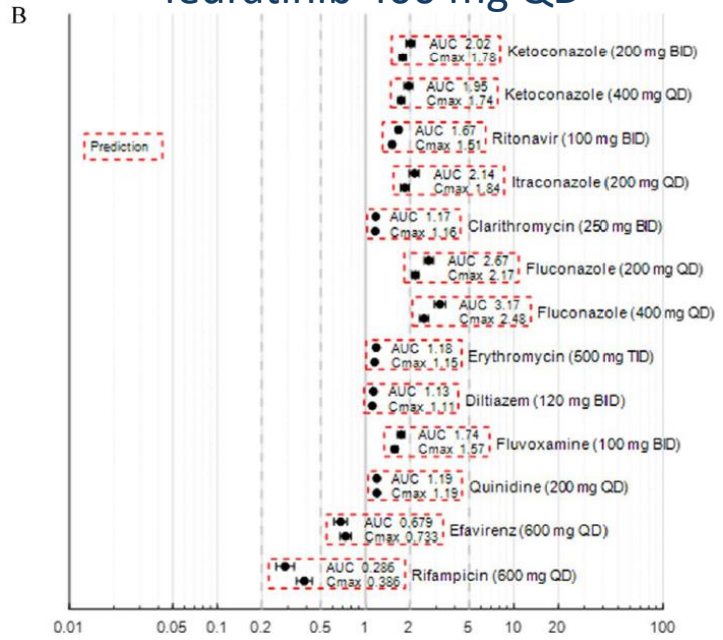
Fedratinib (Inrebic)

Predictions for healthy subjects

fedratinib single dose 300 or 400 mg



fedratinib 400 mg QD



Data from Wu et al, Cancer Chemotherapy & Pharmacology, 2020

Fedratinib (Inrebic)

Regulatory feedback

- Insufficiently validated for CYP3A4 inducers (victim)
- Insufficiently validated for CYP2C19 inhibition (victim for dual inhibition of CYP2C19 and 3A4)
- Insufficiently validated for CYP2C8 and 2C9 inhibition by fedratinib (in vitro data sufficient to exclude a clinically relevant interaction)
- Not sufficient information on transporters
- Model sufficiently validated for prediction of effects of mild to strong CYP3A4 inhibitors
- Initial dose reduction to 200 mg QD with strong CYP3A4 inhibitors
- Effect of strong inhibition of CYP3A4 is maintained long after discontinuation of a strong CYP3A4 inhibitor
    - Stepwise increase after discontinuation (first 2 weeks 300mg OD, then 400 mg fedratinib) yields less increased fedratinib exposure than in case the original 400 mg fedratinib dose is used immediately after stopping the CYP3A4 inhibitor.
- DDI with mild and moderate inhibitors of CYP3A4 are less severe
    - No dose-modification appears necessary for short term use.
    - Caution for prolonged use.

Brigatinib (Alunbrig)

PgP victim interaction

ALK inhibitor, NSCLC, 90mg QD for 7 days, then 180 mg QD

65% excreted in faeces (41% thereof unchanged), 25% in urine (86% thereof unchanged), biliary excretion

2C8 & 3A4 metabolism, substrate and inhibitor of PgP & BCRP

High solubility & permeability

Scope of PBPK:

- Investigation of the mechanism leading to 65% in faeces
- Inhibition of CYP3A4/5 by brigatinib
- Victim of CYP3A4 inhibition & induction, CYP2C8 inhibition

Brigatinib (Alunbrig)

PgP victim interaction

- Model A: unchanged brigatinib in faeces due to unabsorbed drug, fa 0.63
- Model B: complete absorption (fa 1) and biliary clearance
- Predicted c/t profiles and exposures consistent with observed data
- Predicted Cmax and AUC ratios for brigatinib w/o itraconazole within 1.10-fold (A) and 1.04-fold (B) of the observed values
- Predicted Cmax and AUC ratios for brigatinib w/o rifampicin within 1.20-fold (A) and 1.28-fold (B) of the observed values
- Model B: worst-case scenario for P-gp inhibition by assuming that a virtual P-gp inhibitor completely abrogated biliary clearance
    - Brigatinib w/o virtual P-gp inhibitor predicted Cmax and AUC ratios 1.07 and 1.41, respectively.
    - Worst case 41% increase in brigatinib AUC not clinically meaningful in the context of the observed variability in AUC (62% CV).

P-gp and BCRP inhibitors

Brigatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. Given that brigatinib exhibits high solubility and high permeability, inhibition of P-gp and BCRP is not expected to result in a clinically meaningful change in the systemic exposure of brigatinib. No dose adjustment is required for Alunbrig during coadministration with P-gp and BCRP inhibitors.

Brigatinib (Alunbrig)

Other interactions

- Victim of CYP2C8 strong inhibitor gemfibrozil
  - PBPK confirms in vivo data (90 mg brigatinib), predicted Cmax and $AUC_{0\text{-}INF}$ ratios 1.03 and 1.15
- Reversible inhibition of CYP3A4/5 by brigatinib (perpetrator)
  - Midazolam w/o brigatinib predicted Cmax and AUC ratios: 1.07
  - In vivo study recommended due to simultaneous CYP3A4 induction
- Victim of CYP3A4 moderate inhibitors or inducers
  - No uniform dose reduction with inhibitors, but patients should be closely monitored
  - Coadministration of brigatinib with moderate CYP3A inducers should be avoided

Table 27: Comparison of Model-Predicted Geometric Mean C_{max} and $AUC_{0\text{-}INF}$ Ratios for Brigatinib in the Presence versus Absence of Moderate CYP3A Inhibitors or Inducers Using an Unbound Fraction of 0.343 or 0.088

	Unbound Fraction of 0.343		Unbound Fraction of 0.088	
CYP3A Inhibitor/Inducer	C_{max} Ratio	$AUC_{0\text{-}INF}$ Ratio	C_{max} Ratio	$AUC_{0\text{-}INF}$ Ratio
Verapamil	1.08	1.32	1.15	1.38
Diltiazem	1.08	1.40	1.13	1.43
Efavirenz	0.85	0.52	0.83	0.53

IL-6 Mediated Interactions in NMO/NMOSD

Table I. Input Parameter Values Used for IL-6 Model

Parameter	Value	Method/reference
Molecular weight (g/mol)	21,000	(30)
Log *P*	0.01	Assumed
Compound type	Neutral	
B/P	1.00	Assumed
f_u	1.00	Assumed
Main plasma binding protein	Human serum albumin	
Distribution model	Minimal PBPK model	
V_{ss} (L/kg)	0.430	(19)
CL_{iv} (L/h)	1.00	(19)
CL_R (L/h)	0	Assumed
Enzyme	CYP1A2	
E_{min}	0.230	(8)
EC_{50} (μM)	5.96×10^{-5}	(8)
Enzyme	CYP2C9	
E_{min}	0.053	(8)
EC_{50} (μM)	5.76×10^{-6}	(8)
Enzyme	CYP2C19	
E_{min}	0.214	(8)
EC_{50} (μM)	3.40×10^{-6}	(8)
Enzyme	CYP2D6	
E_{min}	0.302	(8)
EC_{50} (μM)	7.19×10^{-6}	(8)
Enzyme	CYP3A4	
E_{min}	0.240	(8)
EC_{50} (μM)	3.48×10^{-6}	(8)
Enzyme	CYP3A5	
E_{min}	0.240	Same values as used for CYP3A4; (8)
EC_{50} (μM)	3.48×10^{-6}	Same values as used for CYP3A4; (8)

- SimCYP v16.1
- IL-6 (perpetrator, steady state) 0, 10, 50 or 100 pg/mL
- Victim drugs: caffeine, S-warfarin, omeprazole, dextromethorphan, simvastatin, and midazolam
- 3 virtual populations: North European Caucasian, Japanese* & Chinese
- 10 virtual trials matching the demographics of the clinical studies
- Observed data from trials with tocilizumab or sirukumab in rheumatoid arthritis
- 10 trials with 10 NMO/NMOSD patients (82% female, 30-46y)

Data from Machavaram et al, AAPS J, 2019
NMOSD: Neuromyelitis Optica Spectrum Disorders
* Updated from default population file

IL-6 Mediated Interactions:

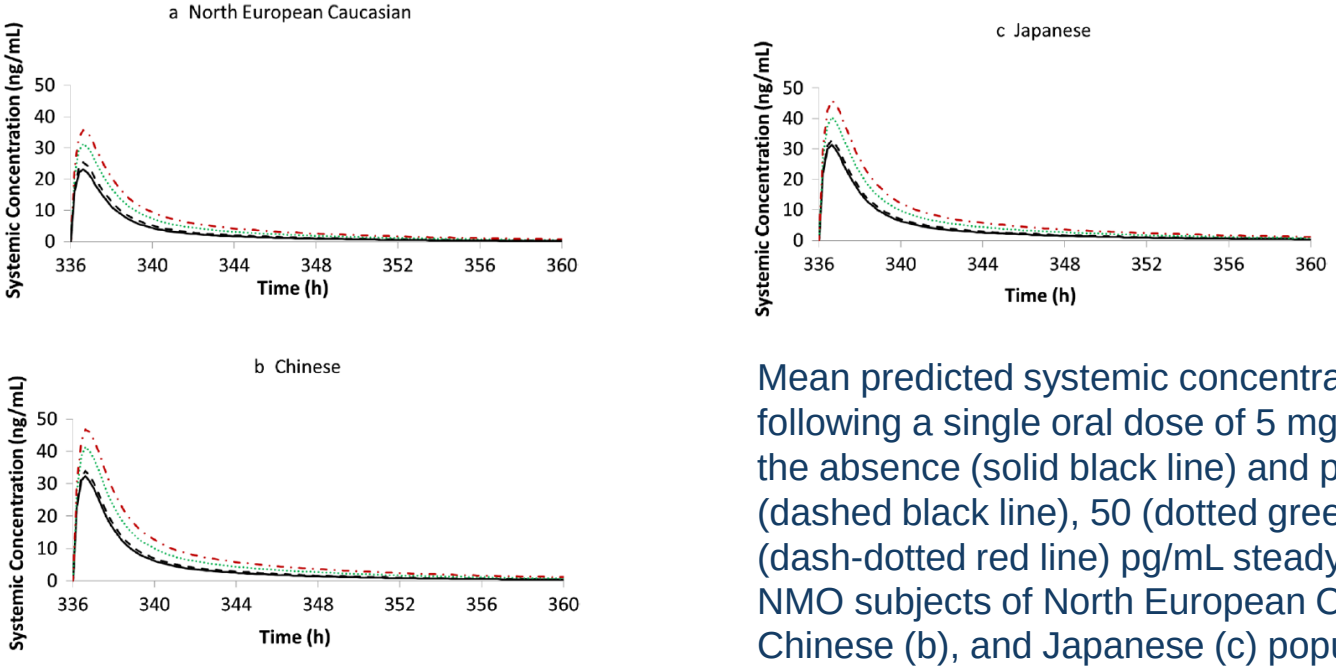
Predicted (100 pg/mL IL-6) vs Observed in Rheumatoid Arthritis Patients

	Predicted mean ± SD	#Observed mean ± SD	Predicted mean fold change (trial range)	#Observed mean fold change
Caffeine (CYP1A2)[b]				
C_{max} (ng/mL)	2380 ± 978	1910 ± 974	1.01 (1.01–1.02)	0.96
AUC (ng.h/mL)	25,000 ± 16,400	15,800 ± 10,000	1.07 (1.04–1.08)	0.89
S-warfarin (CYP2C9)[b]				
C_{max} (ng/mL)	560 ± 215	780 ± 115	1.03 (1.02–1.04)	0.98
AUC (ng.h/mL)	23,100 ± 10,200	24,200 ± 4360	1.33 (1.16–1.37)	1.22
Omeprazole (CYP2C19)[b]				
C_{max} (ng/mL)	493 ± 262	1070 ± 464	1.63 (1.44–1.65)	1.67
AUC (ng.h/mL)	1390 ± 1280	3720 ± 2620	1.92 (1.68–2.02)	1.92
Dextromethorphan (CYP2D6)[c, d]				
C_{max} (ng/mL)	11.1 ± 8.0	2.76 ± 3.17	1.14 (1.11–1.16)	1.27
AUC (ng.h/mL)	186 ± 182	21.9 ± 29.8	1.21 (1.16–1.25)	1.03
Simvastatin (CYP3A)[a]				
C_{max} (ng/mL)	16.4 ± 10.7	36.0 ± 22.0	2.00 (1.82–2.22)	2.57
AUC (ng.h/mL)	70.4 ± 48.3	105 ± 46.0	2.30 (2.07–2.57)	2.36
Midazolam (CYP3A)[b, d]				
C_{max} (ng/mL)	14.0 ± 8.9	17.3 ± 7.8	1.37 (1.28–1.41)	1.34
AUC (ng.h/mL)	52.8 ± 35.0	50.7 ± 24.3	1.63 (1.50–1.72)	1.48

Observed data (N = 12) represents data for CYP probe substrate dosed to rheumatoid arthritis patients 1 week before tocilizumab[a,c] or sirukumab[b] treatment. [d] Predicted data is based on simulations in the presence of 50 pg/mL steady-state IL-6 concentrations. [e] Systemic IL-6 levels span within the range of IL-6 concentrations found in rheumatoid arthritis patients

Data from Machavaram et al, AAPS J, 2019

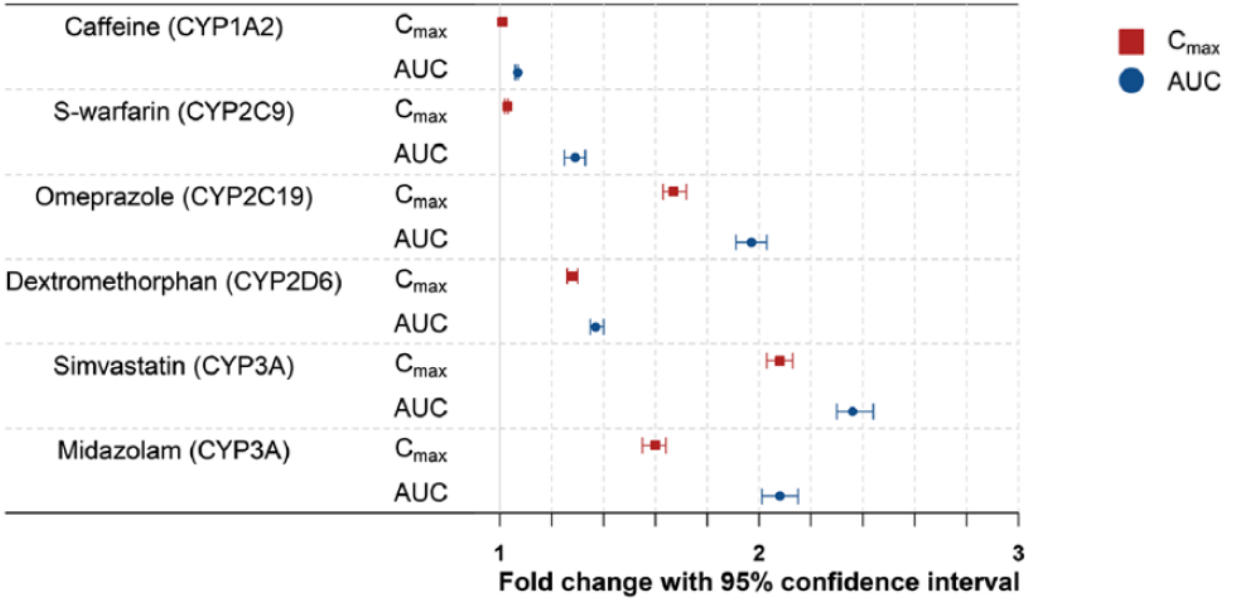
IL-6 Mediated Interactions in NMO/NMOSD



Mean predicted systemic concentrations of midazolam following a single oral dose of 5 mg on day 15 (336 h) in the absence (solid black line) and presence of 10 (dashed black line), 50 (dotted green line), and 100 (dash-dotted red line) pg/mL steady-state IL-6 in virtual NMO subjects of North European Caucasian (a), Chinese (b), and Japanese (c) populations

IL-6 Mediated Interactions in NMO/NMOSD

Predicted geometric mean C_{max} and AUC fold changes (and 95% CIs) for CYP probe substrates in the presence of steady-state IL-6 (100 pg/mL) in virtual NMO subjects of North European Caucasian



Data from Machavaram et al, AAPS J, 2019

IL-6 Mediated Interactions in NMO/NMOSD

Regulatory Issues

Extrapolation between populations with different levels of cytokines remains challenging

Information on the platform qualification required since PBPK is used instead of clinical data (high impact)

Paediatric Extrapolation using PBPK

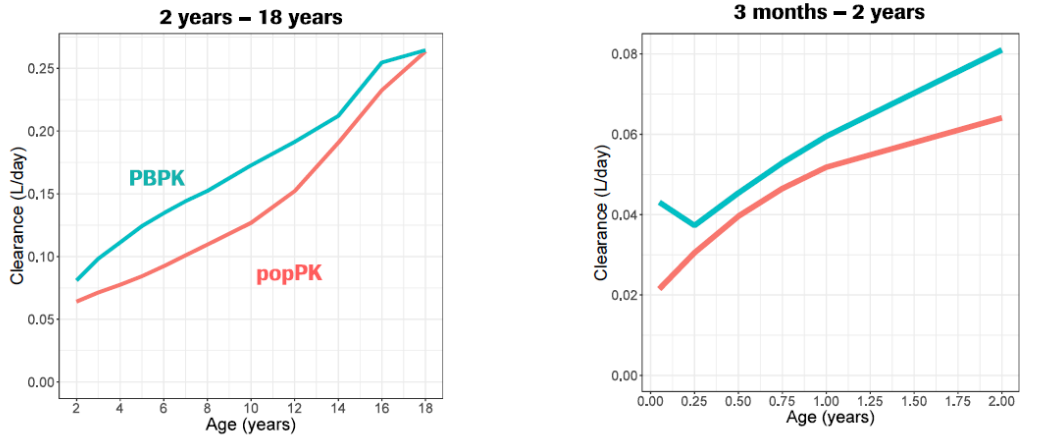
Emicizumab (Hemlibra)

- Support needed for use in children < 2 years old at the time of initial MAA
- PK data in 60 patients < 18y, thereof 10 < 2y and 5 patients 1-2 years
- PopPK: BW (0.75 exponent), albumin and maturation effect on CL/F
- Exposure in neonates is predicted to be 23% (with maturation; AUC_{SS} ~250 µg*day/mL) and 27% (without maturation; AUC_{SS} ~240 µg*day/mL) lower than that observed for of older patients (1–12 years).
- PBPK model supports the range of prediction (medium impact)
- […] the risk, if any, in this patient population [neonates] will be slight under-exposure, however given the exposure-response analysis, this is unlikely to result in lack of efficacy.

Paediatric Extrapolation using PBPK

Emicizumab (Hemlibra)

Larger CL_{PBPK} compared to CL_{POPPK} in an age range where popPK approach adequately describes data



⇒ **Doubt regarding PBPK performances to predict paediatric mAbs PK at its current state.**

Data from Retout et al, PAGE, 2019

Summary & Conclusions

- Interactions remain the most common application of PBPK
- Think about the regulatory impact before writing the PBPK report
- When PBPK is meant to replace clinical data, documentation on platform qualification is often insufficient
- PBPK in paediatric extrapolations for biologics is not as mature as popPK

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References

- EMA, Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. 13 December 2018,
- EMA, Guideline on the investigation of drug interactions, CPMP/EWP/560/95/Rev. 1 Corr. 2** 2012.
- EMA, Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/199678/2016). 2017.
- EMA, Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products, EMA/CHMP/37646/2009. 2012.
- EMA, Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). 2014.
- FDA, Reporting of Computational Modeling Studies in Medical Device Submissions, September 2016
- FDA, Physiologically Based Pharmacokinetic Analyses — Format and Content, August 2018
- V&V40: Assessing Credibility of Computational Models through Verification and Validation: Application to Medical Devices, American Society of Mechanical Engineers Verification and Validation Subcommittee (2018)
- European Public Assessment Reports (EPAR) and Summary of Product Characteristics (SmPC) for Inrebic, Cerdelga, Kisqali, Alunbrig, Mektovi, Lynparza, Braftovi, Enspryng, Polivy, Keytruda, Gamifant, Hemlibra and Blincyto
- Krauss et al. Bayesian Population Physiologically-Based Pharmacokinetic (PBPK) Approach for a Physiologically Realistic Characterization of Interindividual Variability in Clinically Relevant Populations. PLOS ONE (2015) doi:10.1371/journal.pone.0139423
- Luzon et al. Physiologically Based Pharmacokinetic Modeling in Regulatory Decision-Making at the European Medicines Agency. Clinical Pharmacology and Therapeutics (2017) doi:10.1002/cpt.539
- Machavaram et al, Simulating the Impact of Elevated Levels of Interleukin-6 on the Pharmacokinetics of Various CYP450 Substrates in Patients with Neuromyelitis Optica or Neuromyelitis Optica Spectrum Disorders in Different Ethnic Populations, AAPS Journal (2019) 21:42, doi: 10.1208/s12248-019-0309-y
- Parvinian et al, Credibility Evidence for Computational Patient Models Used in the Development of Physiological Closed-Loop Controlled Devices for Critical Care Medicine, Frontiers in Physiology (2019) doi:10.3389/fphys.2019.00220
- Retout et al, A model-based extrapolation enabled labelling of emicizumab in haemophilia A paediatric patients <1 year old despite lack of clinical data, PAGE 28 (2019) Abstr 9089 [www.page-meeting.org/?abstract=9089]
- Wu et al. Physiologically based pharmacokinetic modeling to assess metabolic drug–drug interaction risks and inform the drug label for fedratinib. Cancer Chemother Pharmacol 86, 461–473 (2020). doi: 10.1007/s00280-020-04131-y

Beware of Regulatory Terminology:

Model Verification

EMA

- A part of the qualification focused on the correctness of the mathematical model structure.
- Platform qualification must be documented

FDA

- Information to demonstrate that the PBPK model is appropriate for the modeling purpose (drug product and study population) and is robust enough to respond to perturbations in uncertain parameters
- No platform qualification