

ICH M12 Drug interactions

Emerging areas on drug interaction guidance

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Disclaimer: I attend this conference as an individual expert. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the Medicines Evaluation Board or any of the working parties of the European Medicines Agency EMA or reflecting the position of the Medicines Evaluation Board or EMA.

**GOOD
MEDICINES
USED
BETTER**

[Home](#) | [JAMA](#) | [Vol. 332, No. 7](#)

Medical News in Brief

Study: Polypharmacy Nearly Doubled in 20 Years Among Older Adults in US

More than 4 out of every 10 adults aged 65 years or older reported using 5 or more prescription medications in the past 30 days between 2017 and 2020, according to an **analysis** of cross-sectional survey data from about 14 900 participants. Only about 24% of older people between 1999 and 2000 said they had used 5 or more medications during the past month, which the researchers defined as **polypharmacy**.

The potential for drug interactions for new medicinal products should be evaluated

Scope and goal of the guideline:

- To have global harmonized and systematic, **risk-based approaches** to assess DDIs to avoid regional heterogeneous recommendations in use of new therapeutic products with concomitant drugs
- DDIs of interest for this harmonization effort are **PK-driven and mediated by drug metabolizing enzymes and transporters**

ICH M12 will replace **EMA drug interaction guideline CPMP/EWP/560/95/Rev.1.**

However, there are parts of the EMA drug interaction guideline CPMP/EWP/560/95/Rev.1 that are not covered by ICH-M12 such as food effect, interactions in the gastrointestinal tract, details mass balance.

- Guideline on the investigation of interactions in the gastrointestinal tract
Open for consultation till 31 December 2026
- Guideline on radiolabeled mass balance studies
Will be released soon
- For which medicinal product is a drug drug interaction with oral contraceptives needed?
Clinical pharmacology and pharmacokinetics: questions and answers 2.8
- Reflection paper on the requirements to study the interaction potential of herbal medicinal products
Will be released soon

ICHM12 Guideline on interaction studies

$\frac{C \ B \ G}{M \ E \ B}$



Training on the ICH M12 guideline (EU NTC) 2024

ICH M12 Drug interaction studies: summary of the efforts to achieve global convergence, CPT 2025

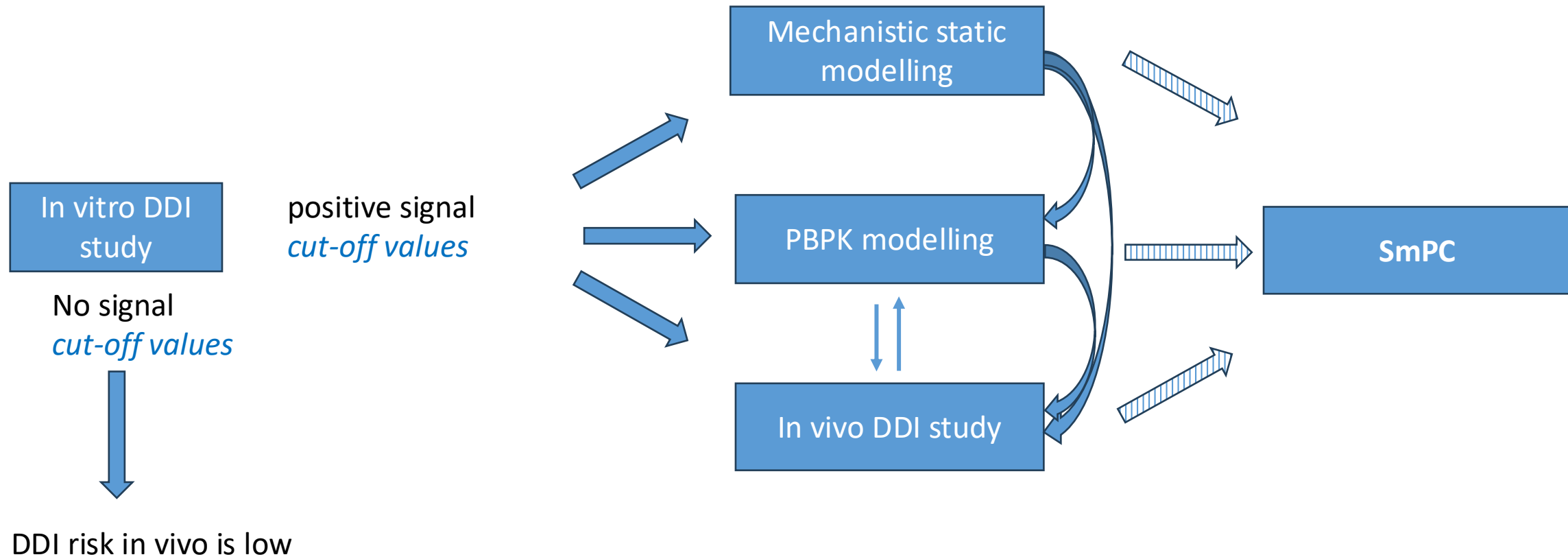
Advances and challenges for drug interaction evaluation - Perspectives on the ICH M12 guideline, CPT 2025

Scientific rationale for the selection of in vitro and in vivo substrates, inhibitors, and inducers in the ICH M12 framework, in prep

ICH-M12 enzyme and transporter mediated interactions

Stepwise, risk based approach

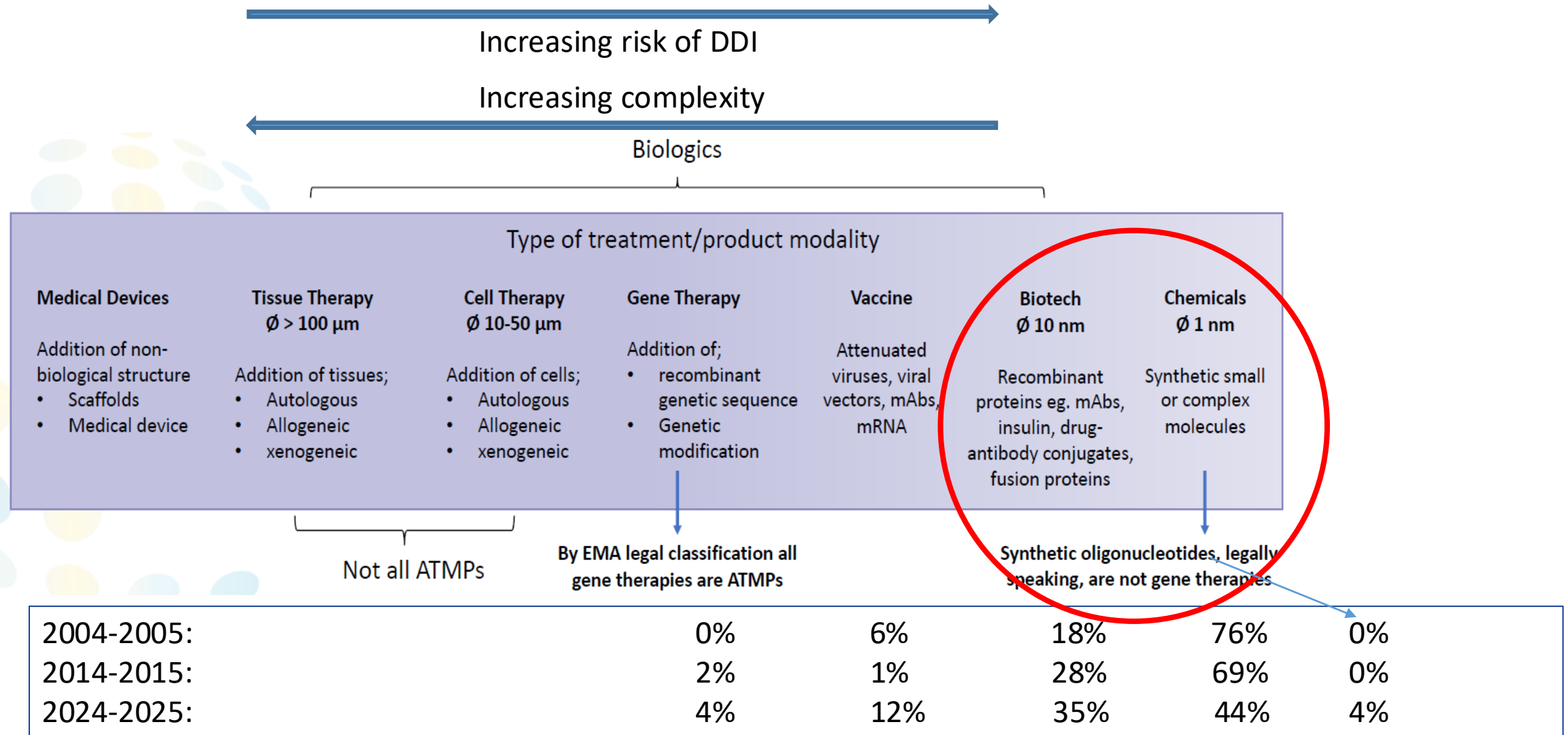
$$\frac{C}{M} \frac{B}{E} \frac{G}{B}$$



- In or out of scope new modality medicinal products
- In vitro study considerations
 - Unbound concentrations
 - Plasma protein binding
 - Non-specific binding
 - Intestinal concentrations / poor solubility drug
- Transporters
- Endogenous substrates

Emerging new medicines and DDI potential

$\frac{C \ B \ G}{M \ E \ B}$



Emerging new medicinal modalities and DDI potential

In vitro in vivo DDI potential

$$\frac{C \quad B \quad G}{M \quad E \quad B}$$

In vitro DDI

Chemicals

- small molecules

✓

Biotech

- Proteins/monoclonal antibodies
- Antibody drug conjugates
 - Antibody
 - Small molecule
 - Precipitant
 - Object

X

X

X

✓

Emerging new medicinal modalities and DDI potential

In vitro in vivo DDI potential

$$\frac{C \quad B \quad G}{M \quad E \quad B}$$

In vitro DDI

Chemicals

- small molecules
- *Peptides*
- *Oligonucleotides*
- *Protacs*

✓
✓ or X
?
Not
discussed

Biotech

- Proteins/monoclonal antibodies
- Antibody drug conjugates
 - Antibody
 - Small molecule
 - Precipitant
 - Object

X

X

X
✓

Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics
Guidance for Industry 2024

[nature](#) > [nature reviews drug discovery](#) > [news in briefs](#) > [article](#)

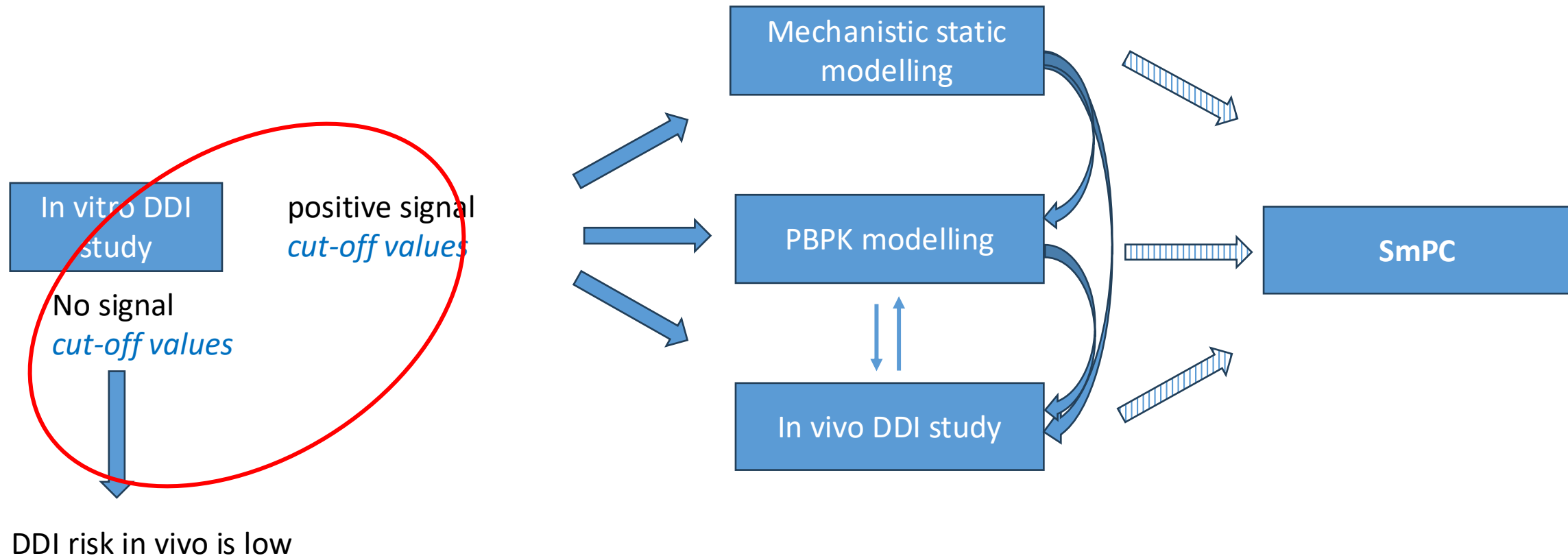
NEWS IN BRIEF | 08 May 2026 | Update [12 May 2026](#)

First PROTAC gains FDA approval, bolstering targeted protein degradation and induced proximity ambitions

ICH-M12 enzyme and transporter mediated interactions

Stepwise, risk based approach

$$\frac{C}{M} \frac{B}{E} \frac{G}{B}$$



Stepwise, risk based approach in vitro in vivo evaluation

$$\frac{C \quad B \quad G}{M \quad E \quad B}$$

in vitro in vivo evaluation (K_{iu} , C_{maxu} , DDI effect in vivo) - cut-off values in vitro assays

- Qualitative evaluation: error matrix
- Quantitative evaluation: static models

Selection criteria for the cut-off values:

- 1) no (low) False Negative rate
- 2) not too high False Positive rate

Re-evaluation of False Negatives:

- In vitro assay condition e.g non-specific binding
- Effect size of in vivo interaction

		Predicted condition	
		Positive (PP)	Negative (PN)
Actual condition	Total population = P + N		
	Positive (P)	True positive (TP)	False negative (FN)
	Negative (N)	False positive (FP)	True negative (TN)

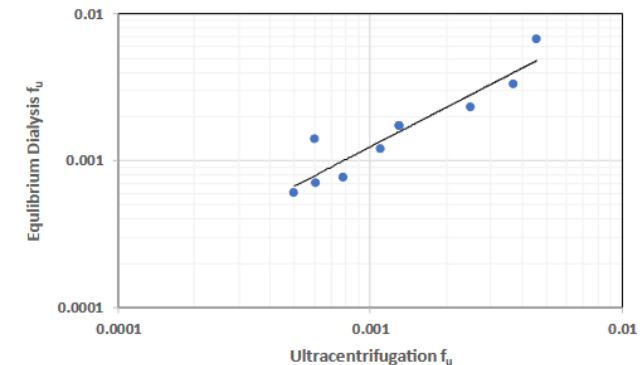
The free drug hypothesis assumes that the free drug is only available to interact with a target receptor or enzyme to exert a pharmacological or toxicological effect

EMA/FDA/PMDA have considered 99% binding as the upper limit of high confidence measurement

- Not sensitive enough methodologies and bioanalytical methods



- Improvement in bioanalytical methods detection drugs at pg/mL possible.
- More methodologies available to measure protein binding with high accuracy and precision which showed *comparable protein binding across methodologies with similar variability for drugs with protein binding > 99% and <99%*



S. Ryu et al. / Journal of Pharmaceutical Sciences 108 (2019) 3745-3749

Measured fraction unbound ($f_{u,p}$) can be used **if**

- Methodology should be suitable for the compound
- Qualify protein binding assay with appropriate positive controls
- Bioanalytical assay have appropriate precision and accuracy at the required sensitivity range
- **A positive control should be included and the positive control should within 3-fold of the mean $f_{u,p}$ value that was previously reported at qualification**
- Novel protein binding assay methodologies should be qualified against an orthogonal method that is previously established and accepted for a range of highly bound compounds

If no compliance to above $\rightarrow f_{u,p} = 0.01$ will be used for >99% protein bound

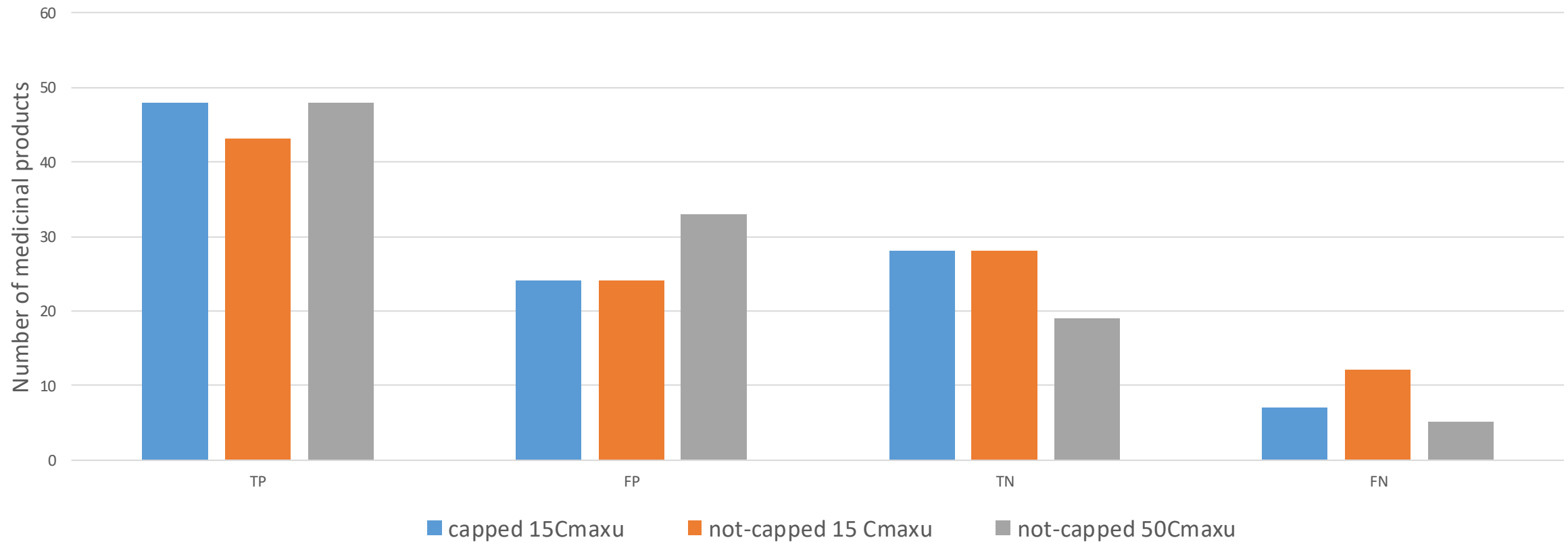
Challenges / discussion points in ICH-M12

High protein binding – compounds with > 99% protein binding

Re-evaluation of the cut-off values with/without capping of fu,p

$$\frac{C \cdot B \cdot G}{M \cdot E \cdot B}$$

In vitro in vivo evaluation for induction with/without capping fu,p



Challenges / discussion points in ICH-M12

In vitro considerations example of induction study

$$\frac{C \quad B \quad G}{M \quad E \quad B}$$

Test compound	Concentration	Mean fold change in mRNA level		
		Donor 1	Donor 2	Donor 3
C123	0.01 μ M	0.827	0.973	0.590*
	0.1 μ M	0.890	0.943	0.557
	1 μ M	0.840	0.920	0.617
	5 μ M	0.880	1.05	0.587
	10 μ M	0.943	1.39	0.663
	20 μ M	0.850	1.87	0.540
	25 μ M	0.900	2.16	0.597
Rifampicin (positive control)	25 μ M	6.56	155*	66.7
Flumazenil (negative control)	25 μ M	1.27	1.40	0.703

- C123 cut-off: $50 \times C_{\max,u} = 1.47 \mu\text{M}$
- Only donor 2 has dose dependent >2-fold mRNA response, however at higher than the cut-of value

→ No in vivo follow-up needed

However, concentration in medium was ~5% of nominal value at end of incubation?

In vitro considerations example of induction study nominal vs binding corrected concentrations

$$\frac{C}{M} \frac{B}{E} \frac{G}{B}$$

F2 analysis for CYP3A4 mRNA induction in on hepatocyte batch

	Nominal concentrations		Binding corrected concentrations	
F2 factor	FP	FN	FP	FN
50	10	1	12	0
30	10	1	12	0
10	5	4	8	0
5	3	11	6	2

Ramsden Eur J of Drug Metabolism and Pharmacokinetics 2022

Challenges / discussion points in ICH-M12

In vitro considerations

$$\frac{C \cdot B \cdot G}{M \cdot E \cdot B}$$

drug	EC50	Emax	In vitro 24h conc % remaining
carbamazepine	59	16	>80%
nifedipine	23	20	<20%-60% conc dep
phenytoin	24	9,5	>50% conc dep
pioglitazone	1,6	7,2	<10% ->75% conc dep
rifampicin	1,0	57	~50%
rifapentine	1,3	44	10-50%
phenobarbital	310	34	>75%
troglitazone	3,2	38	<25%
rosiglitazone	14	13	<20 % conc dep
pleconaril	16	7	30-50%
aprepitant	3,0	8,1	Variable but >75%

Vermet et al. Drug Metab Dispos 2016

Challenges / discussion points in ICH-M12

In vitro considerations

$$\frac{C_B}{M} = \frac{G}{E^B}$$

Measurement of compound remaining in incubation time – what if the concentration is lower than the nominal concentration?

- non-specific binding (materials and cells)
- Precipitation
- Instability in culture medium
- Metabolic instability hepatocytes

Correction
concentration

No correction

Q&A 7.1

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Vermet et al. Drug Metab Dispos 2016

Challenges / discussion points in ICH-M12

Intestinal concentrations and poor solubility drugs

$$\frac{C \quad B \quad G}{M \quad E \quad B}$$

In vitro studies:

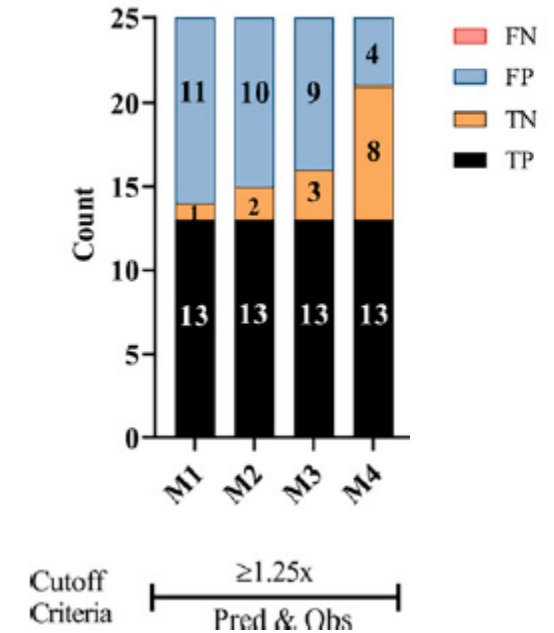
- solubility limits concentration used in assay
- nominal vs actual concentration in assay
- uncertainty in vitro in vivo translation

Interactions in the intestine (inhibition CYP enzymes, transporters)

False positive signal based on in vitro / basic static models

Use of solubility in biorelevant media? Consideration formulation?

Insufficient data for in vitro in vivo evaluation



Tsjeng DMD 2021

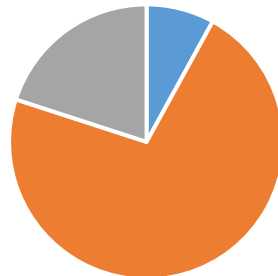
No recommendations for poorly soluble drug substances

Emerging areas / challenges / discussion points in ICH-M12

Investigation of transporter mediated DDI studies

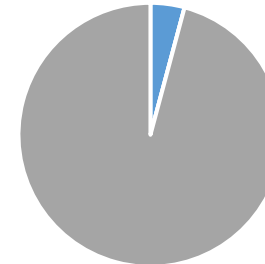
$\frac{C}{M} \frac{B}{E} \frac{G}{B}$

2010-2011
in vitro transporter studied



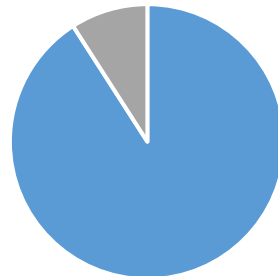
■ 0 ■ 1-3 ■ >3

2020-2021
in vitro transporters studied



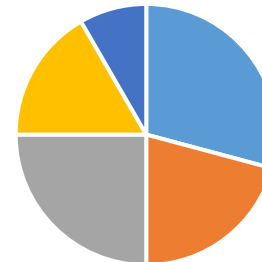
■ 0 ■ 1-3 ■ >3

2010-2011
in vivo studies at MAA



■ Pgp ■ BCRP ■ OATP1B ■ OCT2/MATE ■ OAT

2020-2021
in vivo studies at MAA



■ Pgp ■ BCRP ■ OATP1B ■ OCT2/MATE ■ OAT

Challenges / discussion points in ICH-M12

Investigation of transporter mediated DDI studies



Various transport systems : vesicles, transfected cells, bidirectional transport

Pre-incubation

Correction for non-specific binding

Inhibitor	$C_{max,ss}$ (μM)	f_u	Transporter	$C_{max,u,ss}/IC_{50}$ -pre	$C_{max,u,ss}/IC_{50}$ +pre	Predicted DDI Risk w/o Preincubation		Predicted DDI Risk w/Preincubation	
						FDA/PMDA	EMA	FDA/PMDA	EMA
Cyclosporin A ^a	1.83	0.1	OATP1B1	0.2744	1.8626	Y	Y	Y	Y
			OATP1B3	0.3624	1.0958	Y	Y	Y	Y
Daclatasvir ^b	2.34	0.01	OCT2	0.0003	0.0118	N	N	N	N
			OCT1	0.0439	0.2481	—	Y	—	Y
Dolutegravir ^d	9.9	0.011	OCT2	0.0068	0.0772	N	N	N	Y
Isavuconazole ^e	17.1	0.01	OCT2	0.0102	0.1352	N	N	Y	Y
			MATE1	0.0239	0.0366	Y	Y	Y	Y
			MATE2-K	0.0082	0.0114	N	N	N	N
			OCT1	0.0328	0.0980	—	Y	—	Y
Irinotecan ^f	2.5	0.32	OCT2	0.0140	0.0296	N	N	N	Y
			OCT1	6.6390	35.8744	—	Y	—	Y
Ledipasvir ^g	0.363	<0.01	OCT2	<0.0001	0.0002	N	N	N	N
			OCT1	<0.0001	0.0186	N	N	N	N
Saquinavir ^f	1.41	0.02	OATP1B1	0.0077	0.0275	N	N	N	N
			OATP1B3	0.0026	0.0097	N	N	N	N
			OCT1	0.0015	0.0063	—	N	—	N
Vandetanib ^h	3.32	0.06	OCT2	0.0101	0.0422	N	N	N	Y
			MATE1	0.2509	0.4548	Y	Y	Y	Y
			MATE2-K	0.2264	0.6799	Y	Y	Y	Y
			OCT1	0.0382	0.1027	—	Y	—	Y
Venetoclax ⁱ	2.42	<0.01	OATP1B1	0.0006	0.0365	N	N	N	N
			OATP1B3	<0.0001	0.0007	N	N	N	N

Tatrai et al. Drug Metab Dispos 2019, Omote et al. Sci Rep. 2018

Compounds	$IC_{50}(UDF)$	$IC_{50}(UDF_c)$	$IC_{50}(V)$
Alogliptin	-207.0 ± 91.0	$\sim 207.0 \pm 91.0$	>1000
Amiodarone	10.6 ± 0.6	0.3 ± 0.02	14.8 ± 0.7
Apixaban	>150	>150	>150
Asunaprevir	23.7 ± 3.0	23.7 ± 3.0	3.2 ± 0.2
Atorvastatin	>100	>100	17.0 ± 1.7
Azilsartan	20.9 ± 2.5	4.2 ± 0.5	8.2 ± 0.7
Bosentan	>15	>15	>15

Yabut DMD 2022

use of appropriate in vitro
experimental conditions – details are
important – across model comparison

Challenges / discussion points in ICH-M12

Transporters: extrapolation challenges - classification system

$\frac{C}{M} \frac{B}{E} \frac{G}{B}$

CYP enzymes:

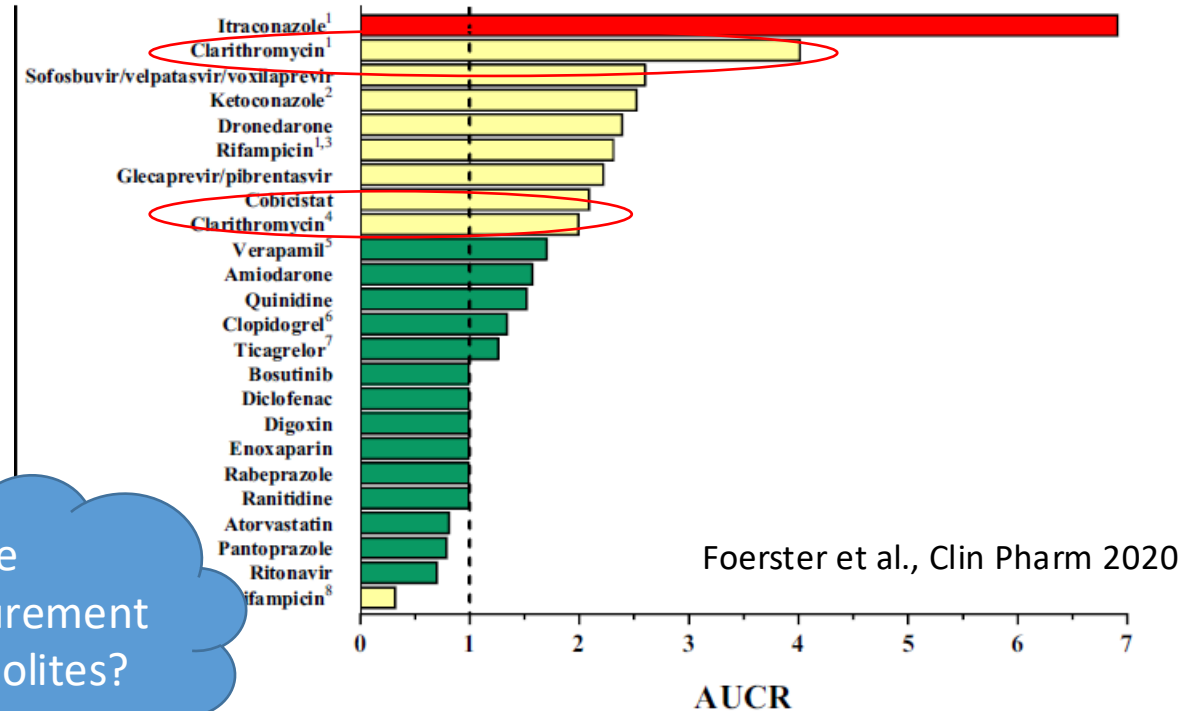
- Mild: 1.25-2 fold increase / decrease
- Moderate: 2-5 fold
- Strong: > 5 fold

Transporters: no classification

Include
endogenous
substrates?

Include
measurement
metabolites?

Dabigatran



- Sensitivity: magnitude of DDIs mediated by transporters or non-CYP enzymes has a more limited range < 3 fold
- Selectivity: interacting mechanisms transporter/transporter and transporter/metabolism
- **In vivo study choice of substrate/perpetrator is typically based on the likelihood of concomitant use for transporters**

Emerging areas / challenges / discussion points in ICH-M12

Metabolites as precipitant – high excretion in faeces

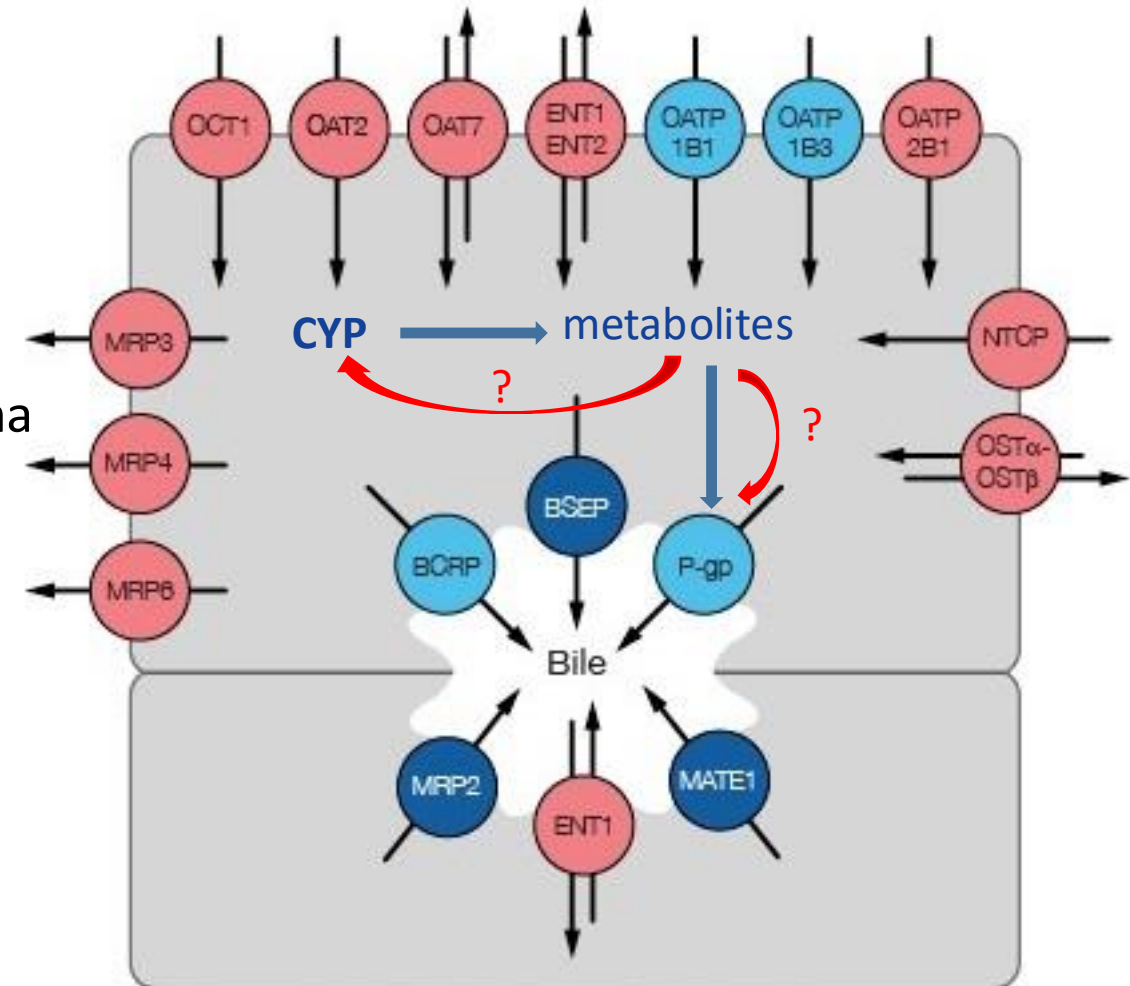
$\frac{C}{M} \frac{B}{E} \frac{G}{B}$

15-20% of new chemical entities had >75% excretion in faeces with moderate to high absorption

metabolites excreted directly in bile

- potential high liver concentrations not reflected in plasma
- liver function / toxicity

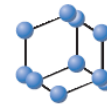
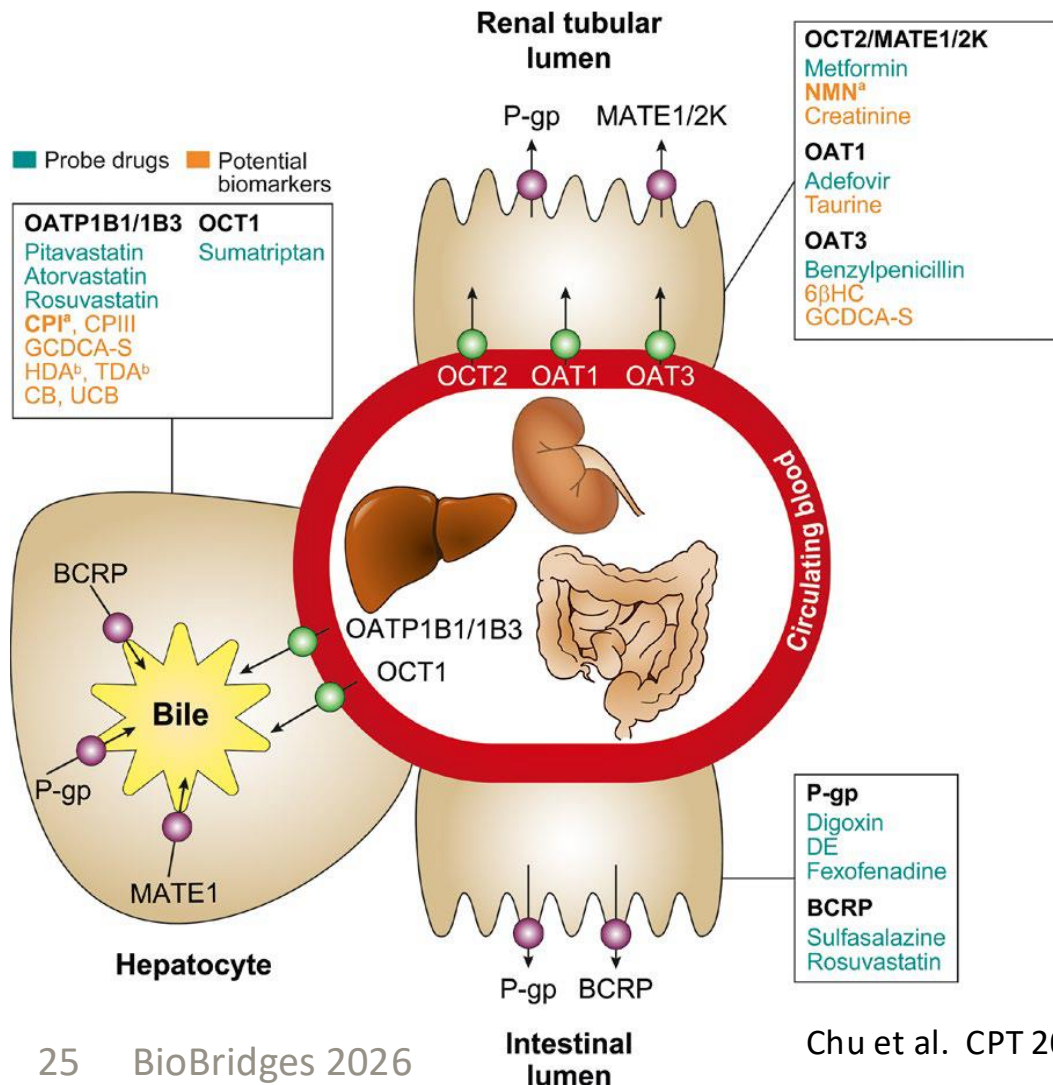
Insufficient data to provide recommendations



Emerging areas / discussion points in ICH-M12

Endogenous substrates

$\frac{C \ B \ G}{M \ E \ B}$



REVIEW ARTICLE

Current Drug Metabolism, 2017, 18, 757-768

Endogenous Biomarkers to Assess Drug-Drug Interactions by Drug Transporters and Enzymes



Endogenous Probes for Drug Transporters: Balancing Vision With Reality

Dose-Dependent Inhibition of OATP1B by Rifampicin in Healthy Volunteers: Comprehensive Evaluation of Candidate Biomarkers and OATP1B Probe Drugs

Review

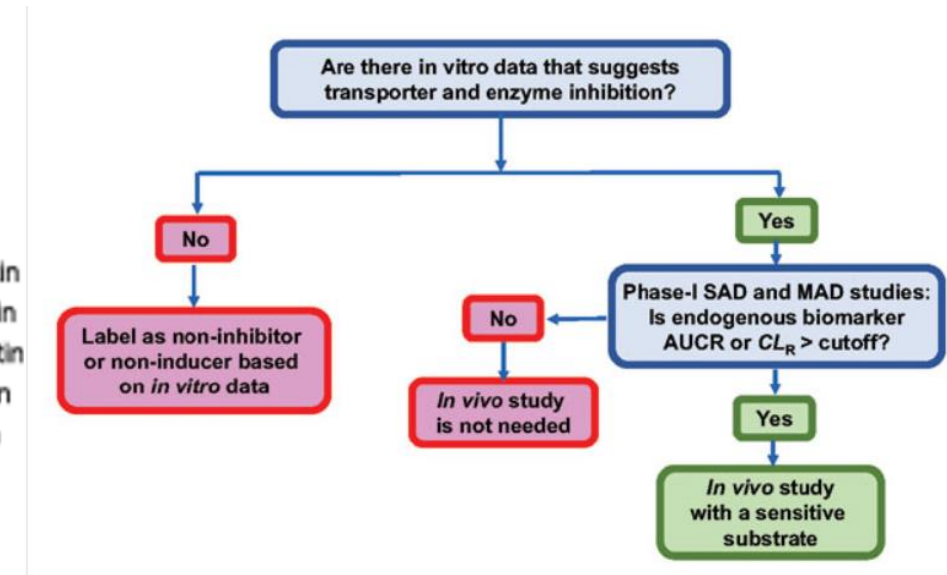
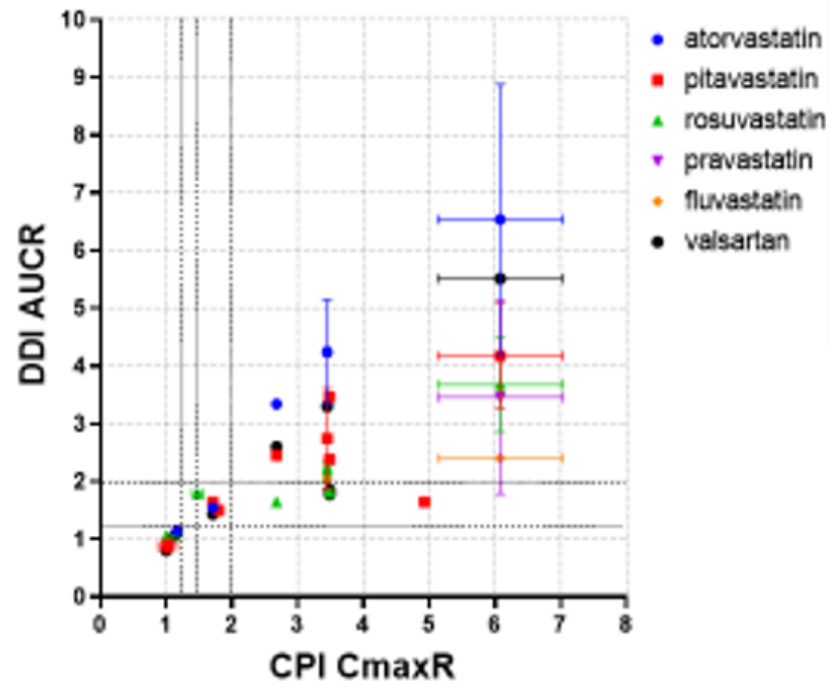
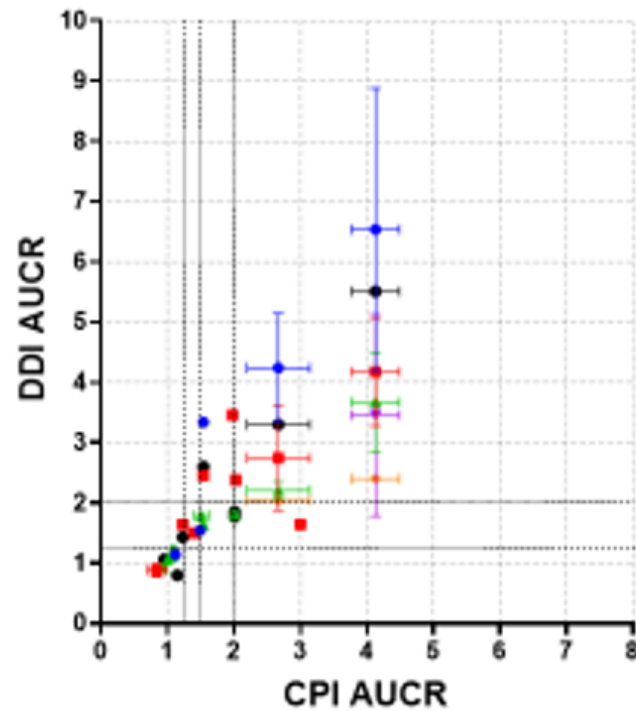
Endogenous Biomarkers for SLC Transporter-Mediated Drug-Drug Interaction Evaluation

Clinical Probes and Endogenous Biomarkers as Substrates for Transporter Drug-Drug Interaction Evaluation: Perspectives From the International Transporter Consortium

Xiaoyan Chu¹, Mingxiang Liao², Hong Shen³, Kenta Yoshida⁴ , Arik A. Zur⁵, Vikram Arya⁶ , Aleksandra Galetin⁷, Kathleen M. Giacomini⁸ , Imad Hanna⁹, Hiroyuki Kusuhara¹⁰, Yurong Lai¹¹ , David Rodrigues¹², Yuichi Sugiyama¹³ , Maciej J. Zamek-Gliszczynski¹⁴, and Lei Zhang¹⁵ on behalf of the International Transporter Consortium

Emerging areas / challenges / discussion points in ICH-M12 endogenous biomarkers - coproporphyrin 1 (CPI) as example

$\frac{C}{M} \frac{B}{E} \frac{G}{B}$

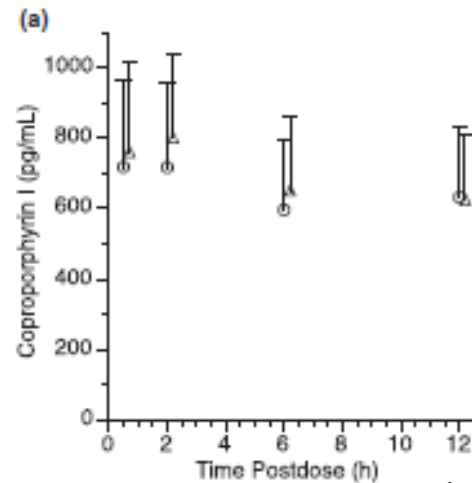
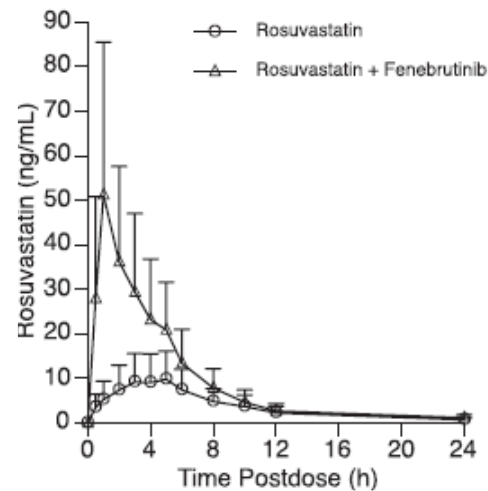


Mariappan et al. Current Drug Metabolism 2017,
Chu et al. CPT 2018,

Emerging areas / challenges / discussion points in ICH-M12 endogenous biomarkers - CPI as example

$\frac{C \ B \ G}{M \ E \ B}$

Fenebrutinib potential inhibitor of BCRP / OATP1B1 /OATP1B3 (IC50 values 9.4/19.7/7.2)
In vivo DDI study with rosuvastatin



Jones et al., CPT 2020

- Use in early dose escalating clinical studies to provide information regarding the drug's potential as an enzyme/ transporter perpetrator
- Use in DDI studies to elucidate mechanism of action

Knowledge caps

- No biomarkers BCRP and Pgp
- Qualification other endogenous biomarkers (ITC paper)
- Endogenous biomarkers in disease populations.

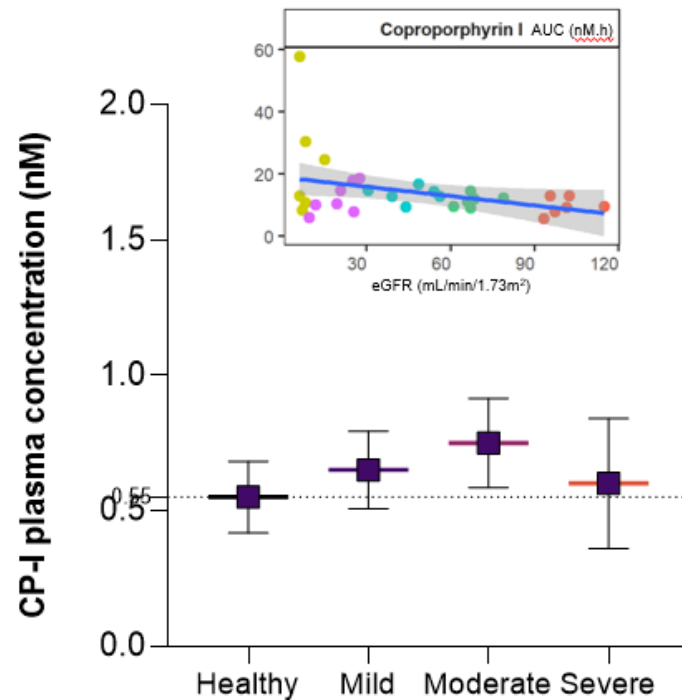
Transporter	Biomarker
OATP1B1/1B3	Coproporphyrin (CP-I)
	Bilirubin
	glycochenodeoxycholate-3-O-sulfate (GCDCA-S)
	Hexadecanedioate (HDA)
OAT1/3	<i>4-pyridoxic acid</i>
	GCDCA-S
	6 β -hydroxycortisol (6bHC)
OCT2/MATE1/2K	<i>N1-methylnicotinamide (NMN)</i>
	N1- methyladenosine
	Creatinine
CYP3A4	4 β -hydroxycholesterol/cholesterol ratio
	6 β -hydroxycortisol/cortisol ratio

Emerging areas / challenges / discussion points in ICH-M12

Endogenous markers CP-1: healthy subjects – special populations

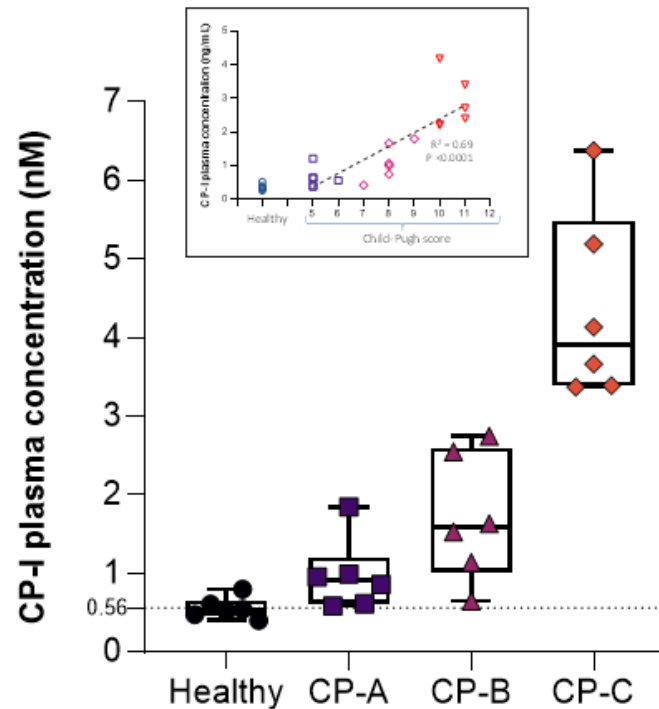
$$\frac{C \quad B \quad G}{M \quad E \quad B}$$

Renal impairment



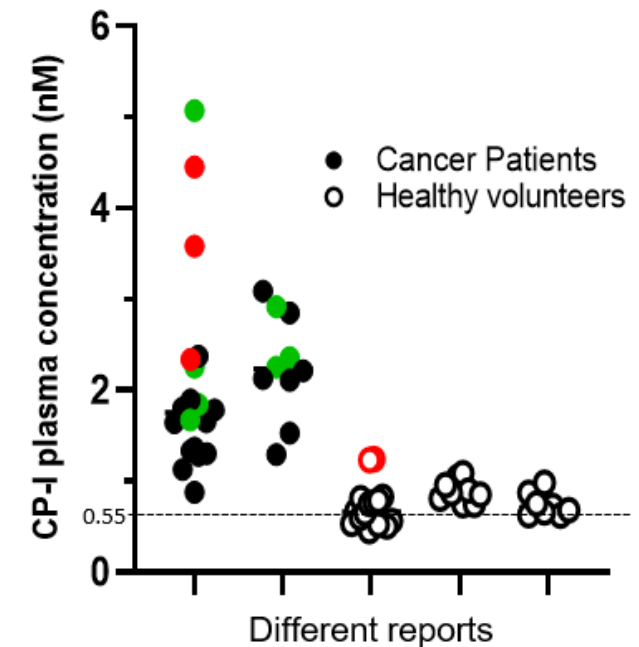
Tatosian D, et al. *Clin Pharmacol Ther.* 2021, 403-415

Hepatic impairment



Lin J, et al. *Clin Pharmacol Ther.* 2023 (Online)

Cancer patients



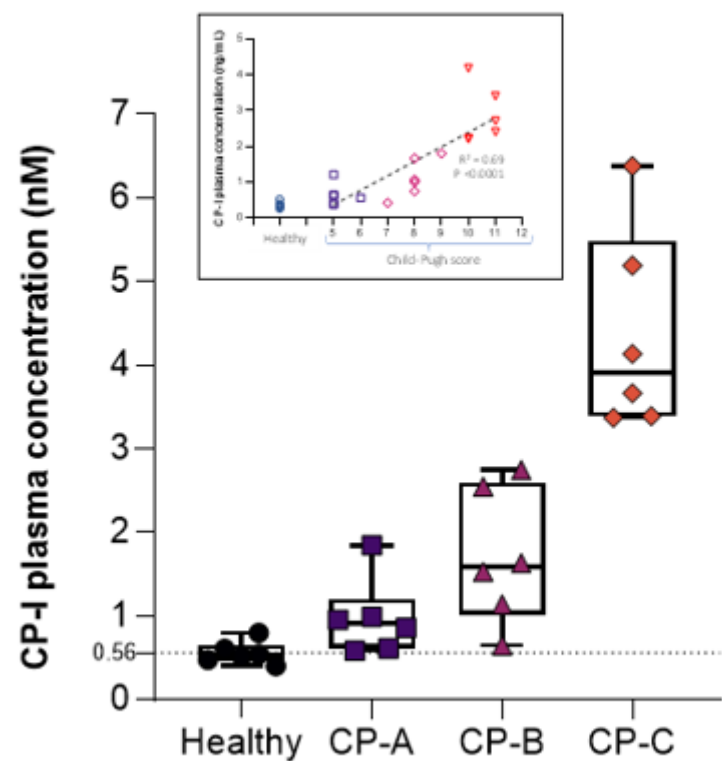
Tsuboya, et al. *Cancer Chemother Pharmacol*, 2001, 543–553.
Mori D et al *Drug Metab Dispos.* 2020, 387-394

Emerging areas / challenges / discussion points in ICH-M12

Endogenous markers: healthy subjects – special populations

$$\frac{C \ B \ G}{M \ E \ B}$$

Hepatic impairment



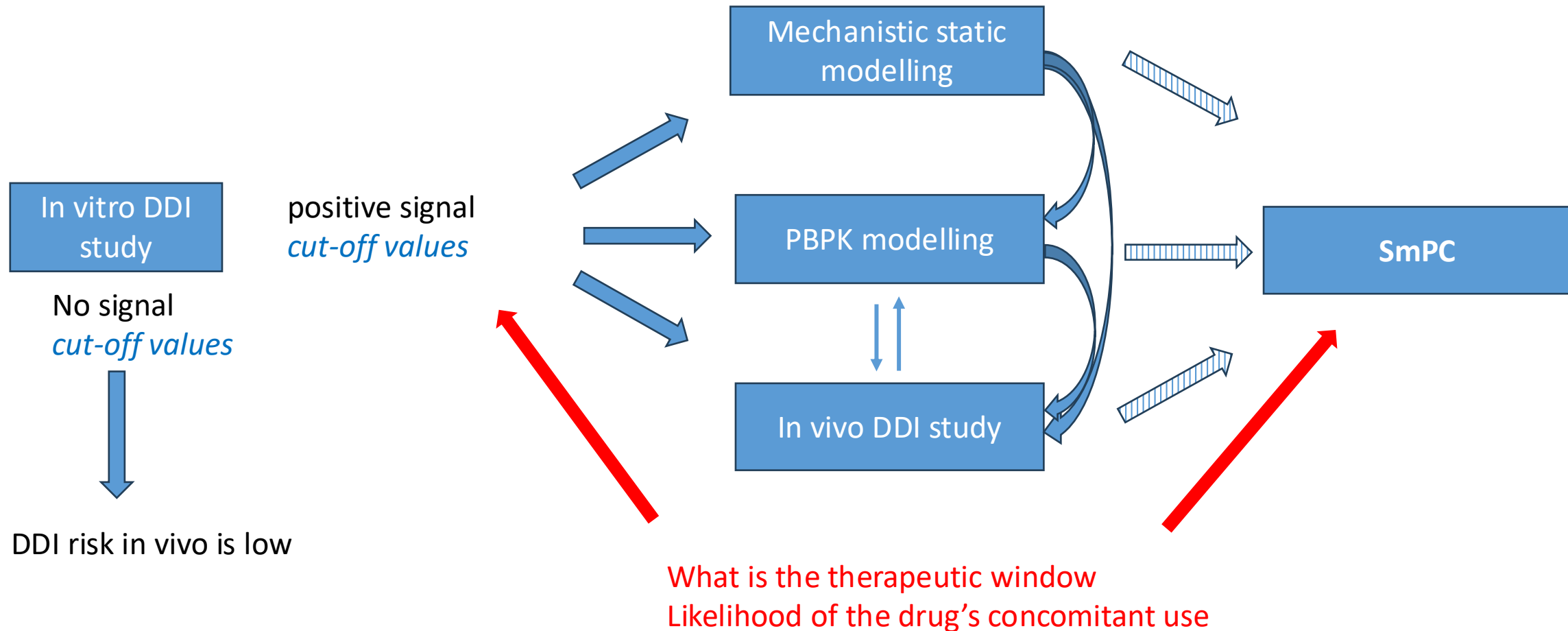
Lin J, et al. Clin Pharmacol Ther. 2023 (Online)

Drug	transporter	Cirrrrhosis	AUC change	Clinical action
rosuvastatin	OATP1B	CP-B CP-C	↑ 2x ↑ 5x	Not recommended
atorvastatin	OATP1B	CP-B CP-C	↑2-4x ↑11x	Dose reduction contraindication
pitavastatin	OATP1B	CP-B CP-C	↑4	Dose reduction contraindication
pravastatin	OATP1B	CP-B	↑1.5	Lower starting dose
valsartan	OATP1B	CP-B	↑2	Dose reduction contraindication

ICH-M12 enzyme and transporter mediated interactions

Stepwise, risk based approach

$$\frac{C}{M} \frac{B}{E} \frac{G}{B}$$



Acknowledgement

$\frac{c \ B \ G}{M \ E \ B}$

Thanks to all members of ICH M12

Elin Lindhagen, Sophie Tseng, and
Demy van der Haak

Members of EMA Translational
Science Office, CPOEG, MWP, QWP,
NcWP, HMPC



EMA Product-Specific Bioequivalence Guidelines (PSBGL) Survey 2027

EMA is developing product-specific bioequivalence guidelines (PSBGLs) for products where applying the current guidelines may not be straightforward. They are drafted by the Clinical Pharmacology Operational Expert Group (CP OEG) of the Methodology Working Party (MWP) at request of CMDh, CHMP or SAWP. Additionally, National Competent Authorities (NCAs) can nominate products via CMDh.

As part of the yearly consultation on its workplan, MWP would like to give their EU Trade Organisations the possibility to highlight their needs in terms of PSBGL guidelines to be developed.

https://forms.cloud.microsoft/Pages/ResponsePage.aspx?id=XMGdvLxhA0-2C-W22JloOdLFvIRYpuJFnx_19TBy0D1UOUdYTEZXSzVDSFJVV1kyWFZPN1ZFNVR YTS4u&fsw=0