

PHARMACOKINETIC DRUG INTERACTIONS WITH DRUGS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION IN 2024: A REVIEW OF CLINICAL DATA AVAILABLE IN NEW DRUG APPLICATION REVIEWS.

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Abstract

In the present work, drug metabolism, drug transport, and drug interaction *in vitro*, in silico, and clinical data for small molecular drugs approved by the U.S. Food and Drug Administration in 2024 (N = 34) were analyzed using Certara Drug Interaction Database (DIDB®; <https://www.druginteractionsolutions.org/>). The mechanism(s) and clinical relevance of these pharmacokinetic interactions were characterized based on information available in the new drug application reviews. When considered as victim drugs, 11 drugs were identified to be clinical substrates based on drug-drug interaction (DDI) studies with cytochrome P450 (CYP) index inhibitors. Among them, 7 drugs were substrates of CYP3A. Vorasidenib and vanzacaftor were the most sensitive substrates, of CYP1A2 and CYP3A respectively, with predicted AUCRs of 10.5 and 10.8 from physiologically based pharmacokinetics (PBPK) modeling and simulations when co-administered with the strong index inhibitors fluvoxamine and itraconazole, respectively. Three drugs were sensitive to CYP3A induction, lazertinib, revumenib, and vanzacaftor, with AUCRs of 0.17-0.19 when co-administered with rifampin, a strong CYP3A index inducer. As inhibitors, 6 drugs were found to be clinical inhibitors of CYP enzymes based on clinical or PBPK results with index substrates. Among them, mavorixafor showed strong inhibition of CYP2D6, resulting in an 8.97-fold increase in dextromethorphan AUC. As inducers, only 2 drugs, elafibranor and tovorafenib, showed induction, with both being weak inducers of CYP3A (simvastatin acid AUCR of 0.68; midazolam predicted AUCR of 0.80). Regarding transporter data, 3 drugs were found to be clinical substrates, including seladelpar (BCRP and OAT3), sulopenem etzadroxil (OAT3), and vadadustat (OAT1/3), with AUCRs of approximately 2 for parent drug or major metabolite when co-administered with probenecid or cyclosporine. As precipitants, 8 drugs were identified as inhibitors of transporters, including P-gp, BCRP, OAT1/3, OATP1B1/1B3, and OCT2 based on clinical evaluations with recommended clinical substrates or endogenous markers. Vadadustat exhibited the highest change in victim exposure, with a 4.58-fold increase in sulfasalazine AUC (BCRP). As expected, all DDIs with AUC changes ≥ 2-fold triggered dosing recommendations in the drugs’ labels. Several DDIs with an AUC change < 2-fold also had label recommendations (mainly monitoring patients for adverse reactions associated with increased drug exposure): for example, resmetirom as a CYP2C8 inhibitor; acoramidis as a CYP2C9 inhibitor; givinostat, lazertinib, and mavorixafor as CYP3A inhibitors; elafibranor and tovorafenib as CYP3A inducers; sulopenem etzadroxil and vadadustat as OAT1/3 substrates; danicopan, mavorixafor, and vanzacaftor/tezacaftor/deutivacaftor as P-gp inhibitors. For nearly half of the approved drugs (N = 15), post-marketing requirements or commitments were issued to evaluate the clinical inhibition potential on CYP2C9, CYP3A, P-gp, BCRP, OATP1B1/3, OCT2, and MATE1, induction potential on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A, and substrate potential of CYP2C8, CYP2D6, CYP3A, UGT, P-gp, BCRP, OATP1B1/3, and MATE1. Overall, CYP3A continued to play a major role in the drug disposition of the drugs in 2024, mediating most of the strong drug interactions, but transporter-mediated clinical interactions seem to be more commonly recognized, irrespective of the drugs’ therapeutic classes.

Objectives

- To review *in vitro* and pharmacokinetic-based clinical DDI data available in the NDA reviews for drugs approved by the FDA in 2024
- To understand main mechanisms that mediate interactions resulting in label recommendations

Methods

- Certara Drug Interaction Database (DIDB; www.druginteractionsolutions.org) was used to identify relevant DDI data. The mechanism(s) and clinical relevance of the interactions were characterized based on information available in the NDA reviews. DDI study results from dedicated DDI clinical trials, pharmacogenetic studies, as well as PBPK modeling predictions performed as alternatives to dedicated clinical studies were examined.
- The classification recommended by the FDA was applied: drug interactions with AUC changes ≥ 5-fold (i.e., AUCRs ≥ 5 or ≤ 0.2), 2- to 5-fold (2 ≤ AUCR < 5 or 0.2 < AUCR ≤ 0.5), or 1.25- to 2-fold (1.25 ≤ AUCR < 2 or 0.5 < AUCR ≤ 0.8) were considered strong, moderate, or weak drug interactions, respectively.

Results

Enzyme-mediated DDIs

- As substrates, 11 drugs among the 34 small new molecular entities (NMEs) approved were identified as clinical substrates based on DDI with inhibitors (**Table 1**):
 - ✓ 2 drugs were sensitive substrates (AUCRs = 10.5-10.8): vorasidenib (CYP1A2) and vanzacaftor (CYP3A), based on PBPK modeling and simulations (highlighted in red)
 - ✓ 6 drugs were moderate sensitive substrates (AUCRs = 2.00-4.53): resmetirom (CYP2C8), deuruxolitinib and seladelpar (CYP2C9), sofipronium (CYP2D6), and mavorixafor and revumenib (CYP3A) (highlighted in orange)
 - ✓ 5 drugs were assessed using PBPK modeling
- 7 drugs were found sensitive to induction of CYP1A2, CYP2C9, and CYP3A to varying extents; 6 were tested with rifampin and 1 drug with carbamazepine (**Table 2**):
 - ✓ 6 drugs were sensitive to CYP3A induction, including 3 drugs with AUCRs of 0.17-0.19 when co-administered with rifampin (highlighted in red)
 - ✓ 1 drug (vorasidenib) was sensitive to CYP1A2 induction
 - ✓ 3 drugs were evaluated using PBPK (rifampin model)
- As inhibitors, 6 drug were confirmed to be clinical inhibitors of CYPs (**Table 3**):
 - ✓ 1 drug (mavorixafor) was a strong CYP2D6 inhibitor, with an AUCR of 8.97 for dextromethorphan (highlighted in red)
 - ✓ 6 drugs showed weak inhibition of CYP2C8, CYP2C9, CYP2E1, and CYP3A
 - ✓ 2 drugs were assessed using PBPK models
- As inducers, 2 drugs showed weak induction (**Table 3**).

Transporter-mediated DDIs

- As substrates, 3 drugs were clinical substrates including seladelpar (BCRP and OAT3), sulopenem etzadroxil (OAT3), and vadadustat (OAT1/3) (**Table 4**) with AUCRs approximately 2.0 for parent and > 2 for major metabolites when co-administered with probenecid or cyclosporine
- As precipitants, 8 drugs were found to be inhibitors of P-gp, BCRP, OAT3, OATP1B1/1B3, and OCT2 using clinical substrates or endogenous biomarkers (**Table 5**). Vadadustat exhibited the highest change in AUC, with a 4.58-fold increase in sulfasalazine exposure, suggesting inhibition of BCRP.
- No transporter induction studies were conducted.

Label impact

- All DDIs with AUCR changes ≥ 2-fold triggered dosing recommendations in the drug labels.
- Some DDIs with an AUC change < 2 also had label recommendations likely pertaining to concomitant use of drugs with a narrow therapeutic index.

Post-marketing requirements or commitments (PMRs or PMCs)

Among the 34 drugs approved, 15 drugs (44%) had PMR or PMCs to further evaluate the drug *in vivo* as substrates (n = 10), inhibitors (n = 10), or inducers (n = 4) of CYPs, UGTs, or drug transporters, indicating existing knowledge gap when drugs were approved.

Table 1. Enzyme-mediated inhibition DDIs with maximum AUCRs ≥ 1.25, NMEs as substrates

NME	Therapeutic Class	Inhibitor	Enzyme	AUCR	Labeling Recommendation
crinecerfont	hormonal replacement therapy	ketoconazole	CYP3A	1.45	none
		itraconazole	CYP3A	1.27	none
deuruxolitinib ¹	antineoplastic agents	fluconazole	CYP2C9, CYP3A	2.40	contraindicated with CYP2C9 strong or moderate inhibitors
		sulfaphenazole	CYP2C9	3.62 ²	
ensifentrine	respiratory system agents	fluconazole	CYP2C9	1.63	none
lazertinib	antineoplastic agents	itraconazole	CYP3A	1.46	none
mavorixafor ¹	immunostimulants	itraconazole	CYP3A	2.00 ³	reduce daily dosage with a CYP3A strong inhibitor; increase the frequency of monitoring for adverse reactions and reduce daily dosage with a CYP3A moderate inhibitor, if necessary; avoid taking dietary supplements that include goldenseal and eating or drinking products with grapefruit
resmetirom	hormonal replacement therapy	clopidogrel	CYP2C8	2.61	not recommended with CYP2C8 strong inhibitors; reduce dose with CYP2C8 moderate inhibitors
revumenib	antineoplastic agents	cobicistat	CYP3A	4.53 ²	reduce dose with a CYP3A strong inhibitor
seladelpar ²	bile and liver therapy agents	itraconazole	CYP3A	1.34 ²	none
		sulfaphenazole	CYP2C9	3.71 ²	avoid CYP2C9 strong inhibitors
sofipronium	anticholinergic	fluconazole	CYP2C9, CYP3A	2.40	monitor for adverse effects in patients with dual CYP2C9 moderate and CYP3A moderate-to-strong inhibitors
vorasidenib	antineoplastic agents	paroxetine	CYP2D6	2.11	avoid CYP2D6 strong inhibitors
vorasidenib	antineoplastic agents	fluvoxamine	CYP1A2	10.5 ²	avoid CYP1A2 strong or moderate inhibitors; if cannot be avoided, monitor for increased adverse reactions and modify the dosage for adverse reactions
vanzacaftor	respiratory system agents	itraconazole	CYP3A	10.8 ²	reduce dose with a CYP3A strong or moderate inhibitor; avoid grapefruit containing product

Studies were performed in healthy subjects; drugs were administered orally; AUCR, AUC ratio; CYP, cytochrome P450; NME, new molecular entity.
¹also a P-gp substrate *in vitro*; ² results obtained from PBPK; ³ results obtained from Product Label: approximation when dose-normalized

Table 2 . Enzyme-mediated induction DDIs with maximum AUCRs ≤ 0.8 , NMEs as substrates

NME	Therapeutic Class	Inducer	Enzyme	AUCR	Labeling Recommendation
crinecerfont	hormonal replacement therapy	rifampin	CYP3A	0.38	increase both the morning and evening doses of 2-fold with CYP3A strong inducers; increase evening dose of 2-fold with CYP3A moderate inducers
deuruxolitinib ¹	antineoplastic agents	rifampin	CYP2C9, CYP3A	0.22	avoid CYP3A strong inducers; avoid CYP2C9 strong or moderate inducers
lazertinib	antineoplastic agents	rifampin	CYP3A	0.17	avoid CYP3A strong or moderate inducers
revumenib	antineoplastic agents	rifampin	CYP3A	0.19 ²	avoid CYP3A strong or moderate inducers
seladelpar ¹	bile and liver therapy agents	carbamazepine	CYP2C9, CYP3A	0.56	monitor biochemical response when initiating rifampin
vorasidenib	antineoplastic agents	rifampin	CYP1A2	0.59 ²	avoid CYP1A2 moderate inducers and smoking tobacco
vanzacaftor	respiratory system agents	rifampin	CYP3A	0.18 ²	not recommended with CYP3A strong or moderate inducers

Studies were performed in healthy subjects; drugs were administered orally; AUCR, AUC ratio; CYP, cytochrome P450; NME, new molecular entity.
¹also a P-gp substrate *in vitro*; ² results obtained from PBPK



• CYP3A continued as the primary contributor to clinically significant interactions.

• Transporter-mediated interactions also played a notable role, accounting for approximately one-third of the observed clinical DDIs, underscoring their growing relevance in drug development and regulatory assessment.

• PBPK modeling was used to assess DDI risk for nearly one-third of the drugs, highlighting the continuously growing role of modeling and simulations in DDI evaluation.



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Additional Results

Table 3. NMEs as inhibitors of enzymes (maximum AUCRs ≥ 1.25) and inducers of enzymes (maximum AUCRs ≤ 0.8)

NME	Therapeutic Class	Substrate	Enzyme	AUCR	Labeling Recommendation
NMEs as inhibitors					
acoramidis	cardiovascular drugs	repaglinide	CYP2C8	1.27 ¹ ; 1.84 ²	none
		tolbutamide	CYP2C9	1.75 ¹ ; 7.98 ²	monitor patients for evidence of increased exposure to CYP2C9 sensitive substrates
enmetazobactam	anti-infective agents	chlorzoxazone	CYP2E1	1.49-1.88 ³ ; 1.85-3.08 ⁴	none
givinostat	neuromuscular blocking agents	midazolam	CYP3A	1.39 ⁵ ; 1.63 ⁶	monitor for orally administered CYP3A sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities
lazertinib	antineoplastic agents	midazolam	CYP3A	1.47 ⁷ ; 1.60 ⁸	monitor for adverse reactions associated with a CYP3A substrate where minimal concentration changes may lead to serious adverse reactions
mavorixafor	immunomodulators	dextromethorphan	CYP2D6	8.97	contraindicated with drugs that are highly dependent on CYP2D6 for clearance
		midazolam	CYP3A	1.72	monitor for CYP3A substrate related adverse reactions more frequently where minimal substrate concentration changes may lead to serious adverse reactions, unless otherwise recommended in the substrate prescribing information
resmetirom	hormone replacement therapy	pioglitazone	CYP2C8	1.45	monitor patients more frequently for substrate-related adverse reactions where minimal concentration changes may lead to serious adverse reactions
NMEs as inducers					
elafibranor	bile and liver therapy agents	simvastatin lactone	CYP3A	0.99; 0.68 ⁹	switch to effective non-hormonal contraceptives or add a barrier method when using hormonal contraceptives during treatment and for at least 3 weeks after last dose
tovorafenib	antineoplastic agents	midazolam	CYP3A	0.80 ²	avoid CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures; if unavoidable, monitor patients for loss of efficacy unless otherwise recommended in the prescribing information for CYP3A substrates

Studies were performed in healthy subjects; drugs were administered orally; AUCR, AUC ratio; CYP, cytochrome P450; NME, new molecular entity.
¹ results obtained from PBPK; ² results obtained from PBPK prediction with 10-fold reduced K_m value; ³ results obtained from PBPK prediction assuming that chlorzoxazone was metabolized 60% (fm = 0.6) by CYP2E1; ⁴ results obtained PBK prediction assuming that chlorzoxazone was metabolized 90% (fm = 0.9) by CYP2E1; ⁵ results obtained on Day 3; ⁶ results obtained on Day 14; ⁷ performed in subjects with GSTM1 wild-type genotype; ⁸ performed in subjects with GSTM1 null genotype; ⁹ simvastatin acid

Table 4. NMEs as substrates of transporters with maximum AUCRs ≥ 1.25

NME	Therapeutic Class	Inhibitor	Transporter	AUCR	Labeling Recommendation
seladelpar	bile and liver therapy agents	probenecid	OAT3	2.00, 3.40 ¹ , 8.12 ² ; 6.70 ³	avoid OAT3 inhibitors
		cyclosporine	BCRP	2.09, 1.0 ¹ ; 1.25 ²	closely monitor patients for adverse effects with concomitant administration of drugs that inhibit BCRP
sulopenem etzadroxil	anti-infective agents	probenecid	OAT3	1.79	monitor more frequently for adverse reactions associated with sulopenem etzadroxil/probenecid if concomitantly used with drugs that inhibit OAT3
vadadustat	antianemic	probenecid	OAT1, OAT3	1.82, 2.26 ⁴	closely monitor for too large or too rapid an increase in hemoglobin response and for adverse reactions if OAT1/3 inhibitors are co-administered

Studies were performed in healthy subjects; drugs were administered orally; AUCR, AUC ratio; BCRP, breast cancer resistance protein; NME, new molecular entity; NP, not provided; OAT, organic anion transporter.
¹ seladelpar sulfoxide (M1); ² O-desethylseladelpar (M2); ³ O-desethylseladelpar sulfoxide (M3); ⁴ vadadustat-O-glucuronide

Table 5. NMEs as inhibitors of transporters with maximum AUCRs ≥ 1.25

NME	Therapeutic Class	Substrate	Transporter	AUCR	Labeling Recommendation
arimoclomol	nervous system agent	endogenous creatinine	OCT2	1.19	monitor for adverse reactions and reduce dosage of OCT2 substrates; use alternative measures that are not based on creatinine to measure renal function
danicopan	immunomodulators	fexofenadine	P-gp	1.62	adjust dose for P-gp substrates where minimal concentration changes may lead to serious adverse reactions
		rosuvastatin	BCRP	2.25	monitor for adverse reactions associated with the BCRP substrate and consider dose reduction of the BCRP substrate; dose of rosuvastatin should not exceed 10 mg once daily
givinostat	neuromuscular blocking agents	endogenous creatinine	OCT2	1.25	closely monitor when used in combination with drugs known as sensitive substrates of OCT2 for which a small change in substrate plasma concentrations may lead to serious toxicities
lazertinib	antineoplastic agents	rosuvastatin	BCRP	2.02	monitor for adverse reactions associated with a BCRP substrate where minimal concentration changes may lead to serious adverse reactions
mavorixafor	Immunomodulators	digoxin	P-gp	1.65	monitor for P-gp substrate adverse reactions where minimal substrate concentration changes may lead to serious adverse reactions; measure serum digoxin concentrations before initiating mavorixafor and monitor digoxin concentrations
resmetirom	hormone replacement therapy	atorvastatin	OATP1B1, OATP1B3	1.39; 1.76 ³	adjust dose for certain statins: limit atorvastatin and pravastatin to 40 mg once daily; monitor for statin-related adverse reactions
		rosuvastatin	BCRP, OATP1B1, OATP1B3	1.82	adjust dose for certain statins: limit rosuvastatin and simvastatin total daily dose to 20 mg; monitor for statin-related adverse reactions
vadadustat	antianemic	atorvastatin	OATP1B1	1.42; 1.68 ⁴	none
		rosuvastatin	BCRP, OATP1B1	2.47	monitor statin-related adverse reactions; the maximum daily dose of rosuvastatin should not exceed 5 mg and the starting dose of simvastatin should be 5 mg/day (maximum daily dose of 20 mg)
		sulfasalazine	BCRP	4.58	monitor for signs of adverse effects of BCRP substrates and reduce substrate dosage in accordance
		furosemide	OAT3	2.09	monitor for adverse reactions of OAT3 substrates and adjust substrate dosage in accordance
tezacaftor/ ivacaftor	respiratory system agents	digoxin	P-gp	1.30	monitor frequently for adverse reactions for P-gp substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the P-gp substrate prescribing information

Studies were performed in healthy subjects; drugs were administered orally; AUCR, AUC ratio; BCRP, breast cancer resistance protein; NME, new molecular entity; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein.
¹C_{max} ratio; ² C_{avg} ratio; ³ atorvastatin lactone; ⁴ para-hydroxyatorvastatin