MECHANISTIC STUDIES SUPPORTING THE EVALUATION OF PHARMACOKINETIC-DRUG INTERACTIONS WITH DRUGS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION IN 2023: A SYSTEMATIC REVIEW OF NEW DRUG APPLICATIONS

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Abstract

The mechanistic evaluation of enzyme- and transporter-based drug-drug interactions (DDIs) is an integral part of the drug development process and supports the safe and effective clinical use of new therapies. In the present work, DDI data for small molecular drugs approved by the U.S. Food and Drug Administration in 2023 (N = 38) were analyzed using Certara Drug Interaction Database (https://www.druginteractionsolutions.org/). The mechanism(s) and clinical magnitude of the observed interactions were characterized based on information available in the new drug application reviews. DDI data from dedicated clinical trials, pharmacogenetics studies, physiologically-based pharmacokinetics (PBPK) modeling and simulations, and population PK analyses were examined. Positive study results defined as mean area under the curve ratios (AUCRs) ≥ 1.25 for inhibition DDIs and ≤ 0.8 for induction DDIs, were then fully analyzed. When new drugs were evaluated as victims of enzyme-based DDIs, a total of 23 drugs (61%) were affected by perpetrator drugs (through inhibition and/or induction). Seven drugs were found to be sensitive substrates of CYP1A2 (fezolinetant), CYP2C8 (daprodustat), and CYP3A (elacestrant, gepirone, nirmatrelvir, nirogacestat, and repotrectinib), with AUCRs of 5.27-18.60 when co-administered with the strong marker inhibitors fluvoxamine, gemfibrozil, itraconazole, or ketoconazole. Four drugs, leniolisib, omaveloxolone, palovarotene, and sparsentan were found to be moderate sensitive substrates of CYP3A (AUCRs 2.12-4.12 with co-administration of itraconazole or ketoconazole). Regarding transporters, only three drugs, iptacopan (P-gp, BCRP, OATP1B1/1B3), momelotinib (OATP1B1/1B3), and zavegepant (OATP1B3, NTCP), were clinical substrates of transporters, with a maximum AUCR of 2.39 predicted for zavegepant using PBPK modeling and simulations following single-dose rifampin administration. As perpetrators, only one combination drug, nirmatrelvir and ritonavir, was considered a strong inhibitor of CYP3A (midazolam AUCR 14.30). No drug exhibited strong inhibition of transporters. The following four drugs were found to be moderate inhibitors (marker substrates AUCRs 2.07-2.73): momelotinib (BCRP), nirogacestat (CYP3A), pirtobrutinib (BCRP, CYP2C8), ritlecitinib (CYP1A2, CYP3A). No strong inducer of enzymes or transporters was identified. Four drugs showed enzyme induction, with repotrectinib showing the maximum induction and considered a moderate inducer of CYP3A (midazolam AUCR 0.31). As expected, almost all DDIs (except one) with AUCRs ≥ 2 or ≤ 0.5 (≥ 2-fold change) triggered dosing recommendations in the product labels. PBPK modeling and simulations continued to be increasingly used in lieu of clinical trials, with 12 drugs evaluated as victims of enzymes (N = 11) or transporter (N = 1), and 5 drugs as inhibitors of enzymes (N = 4) or transporters (N = 1). In line with the trend observed in recent years, oncology was the most represented therapeutic area, including 24% of all 2023 approvals. However, drugs found to be either sensitive substrates or strong inhibitors of enzymes included treatments for a variety of diseases, e.g., cancer treatments, antianemia preparations, anti-estrogens, antidepressants, and antivirals. This finding highlights the continuous challenge of effectively managing the risk of significant pharmacokinetic interactions in the clinic in patient populations who often receive numerous concomitant medications.

Objectives

- To review *in vitro* and pharmacokinetic-based clinical DDI data available in the NDA reviews for drugs approved by the FDA in 2023
- 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 and simulations that functioned as alternatives to dedicated clinical studies were examined.
- Applying the categorization recommended by the FDA, any 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

- Among the small new molecular entities (NMEs) approved (N = 38), 21 drugs were identified as clinical substrates based on DDI studies with inhibitors (**Table 1**):
  - 7 drugs were sensitive substrates (AUCRs = 5.27-18.60), including 5 for CYP3A, 1 for CYP1A2, and 1 for CYP2C8 (highlighted in red)
  - 4 drugs were moderate sensitive substrates (AUCRs = 2.12-4.12), all for CYP3A (highlighted in orange)
  - 1 drug was assessed using PBPK (probenecid model)
- 17 drugs were found sensitive to induction:
  - 16 drugs were sensitive to CYP3A induction, with AUCRs of 0.03-0.51 when co-administered with CYP3A inducers rifampin (N = 14), carbamazepine, or efavirenz
  - 1 drug was sensitive to CYP1A2 induction by cigarette smoking
  - 5 were assessed using PBPK (rifampin model)
- As inhibitors, 10 drug were confirmed to be clinical inhibitors of CYPs (**Table 2**):
  - 1 drug was a strong CYP3A inhibitor (highlighted in red)
  - 3 drugs showed moderate inhibition of CYP1A2, CYP2C8, and CYP3A (highlighted in orange)
  - 3 drugs were assessed using PBPK models
- As inducers, 4 drugs showed weak-to-moderate induction (**Table 3**).

Transporter-mediated DDIs

- As substrate, 3 drugs were clinical substrates of transporters, with a maximum AUCR of 2.39 for zavegepant using PBPK following single-dose rifampin (**Table 4**).
- As perpetrator, no drug exhibited strong inhibition of transporters. 6 drugs were found to be clinical inhibitors, with maximum AUCRs of 2.40-2.73 (rosuvastatin) for 2 drugs, suggesting BCRP inhibition (**Table 5**).
- No transporter induction studies were conducted.

Label impact

- All DDIs with AUC 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.

Table 1. Enzyme-mediated inhibition DDIs, NMEs as substrates

NME	Therapeutic Class	Inhibitor	Enzyme	AUCR	Label Recommendation
bexagliflozin	diabetes treatments	probenecid	UGT1A9	1.39	none
capivasertib	antineoplastic agents	itraconazole	CYP3A[1]	1.95	**avoid** strong CYP3A inhibitors
		probenecid	UGT2B7	1.36[2]	none
daprodustat	antianemic preparations	gemfibrozil	**CYP2C8**	**18.60**	**contraindicated** with strong CYP2C8 inhibitors
elacestrant	antineoplastic agents	itraconazole	**CYP3A**	**5.27**	**avoid** strong or moderate CYP3A inhibitors
etrasimod	immunosuppressants	fluconazole	CYP2C9, CYP3A	1.84	**not recommended** with moderate to strong inhibitors of CYP2C9 and CYP3A
		gemfibrozil	CYP2C8	1.36	none
		itraconazole	CYP3A	1.32	
fezolinetant	other gynecologicals	fluvoxamine	**CYP1A2**	**9.39**	**contraindicated** with CYP1A2 inhibitors
gepirone	nervous system	ketoconazole	**CYP3A**	**6.05**	**contraindicated** with strong CYP3A inhibitors
iptacopan	immunosuppressants	clopidogrel	CYP2C8	1.36	**not recommended** with strong CYP2C8 inhibitors
leniolisib	immunomodulators	itraconazole	CYP3A[1]	2.12	**avoid** strong CYP3A inhibitors
nirmatrelvir	antivirals	ritonavir	**CYP3A**	**8.31**	none (combination drugs)
nirogacestat	antineoplastic agents	itraconazole	**CYP3A[1]**	**8.23**	**avoid** strong CYP3A inhibitors
omaveloxolone	nervous system	itraconazole	CYP3A[1]	4.12	**avoid** strong CYP3A inhibitors
palovarotene	musculo-squeletal system agents	ketoconazole	CYP3A	3.11	**avoid** strong CYP3A inhibitors, grapefruit, pomelo, or juices containing these fruits
pirtobrutinib	antineoplastic agents	itraconazole	CYP3A[1]	1.49	**avoid** strong CYP3A inhibitors or reduce pirtobrutinib dosage
quizartinib	antineoplastic agents	ketoconazole	CYP3A	1.94	**reduce dosage** with strong CYP3A inhibitors
repotrectinib	antineoplastic agents	itraconazole	**CYP3A[1]**	**5.90**	**avoid** strong or moderate CYP3A inhibitors
sotagliflozin	cardiovascular system	mefenamic acid	UGT1A9	1.77	none
sparsentan	other therapeutic products	itraconazole	CYP3A[1]	2.72	**avoid** strong CYP3A inhibitors
vamorolone	corticosteroid	itraconazole	CYP3A	1.44	**reduce dosage** with strong CYP3A inhibitors
zavegepant	migraine agents	itraconazole	CYP3A[1]	1.59	none
zuranolone	nervous system	itraconazole	CYP3A	1.62	**reduce dosage** with strong CYP3A inhibitors

[1] P-gp substrate *in vitro* [2] based on PBPK modeling and simulations

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- CYP3A played a major role in the disposition of 18 out of 38 drugs (47%), with 5 of these being sensitive substrates.
- CYP3A was also the most affected enzyme, with 6 drugs showing inhibition and 3 showing induction of CYP3A.
- PBPK was used to evaluate enzyme-mediated DDIs, including 5 drugs evaluated as substrates and 4 as inhibitors.
- Transporter-mediated DDIs mostly involved OATP1B (NMEs as substrates) and P-gp/BCRP (NMEs as inhibitors).

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Additional Results

Table 2. Enzyme-mediated DDIs, NMEs as inhibitors

NME	Substrate	Enzyme	AUCR	Label Recommendation
bexagliflozin	glimepiride	not identified	1.27	none
capivasertib	desipramine	CYP2D6	1.50[1]	none
	raltegravir	UGT1A1	1.72[1]	
	midazolam	CYP3A	1.77	
etrasimod	ethinylestradiol and levonorgestrel	not identified	1.24 (ethinylestradiol) 1.32 (levonorgestrel)	none
leniolisib	ethinylestradiol	CYP3A	1.32	none
nirmatrelvir and ritonavir	midazolam	**CYP3A**	**14.30**	**contraindicated** with drugs primarily metabolized by CYP3A and for which elevated concentrations are associated with serious and/or life-threatening reactions
nirogacestat	midazolam	**CYP3A**	**2.07[1]**	**avoid** CYP3A substrates where minimal concentration changes may lead to serious adverse reactions
pirtobrutinib	repaglinide	**CYP2C8**	**2.30**	concomitant use of sensitive substrates of CYP2C8, CYP2C19, and CYP3A may increase the risk of adverse events related to these substrates for drugs which are sensitive to minimal concentration changes
	omeprazole	CYP2C19	1.56	
	midazolam	CYP3A	1.70	
ritlecitinib[2]	midazolam	**CYP3A**	**2.69**	additional **monitoring** and dose adjustment of CYP3A and CYP1A2 substrate where small concentration changes may lead to serious adverse reactions
	caffeine	**CYP1A2**	**2.65**	
sotagliflozin	ramipril	not identified	1.88	none
trofinetide	midazolam	CYP3A	1.33[1]	**monitor** for adverse reactions of orally CYP3A sensitive substrates for which minimal concentration may lead to serious toxicities

[1] based on PBPK modeling and simulations; [2] administered at a high dose of 200 mg once daily while the clinical dose is 50 mg once daily

Table 3. Enzyme-mediated DDIs, NMEs as Inducers

NME	Substrate	Enzyme	AUCR	Label Recommendation
omaveloxolone	midazolam	CYP3A	0.55	refer to the prescribing information of substrates of CYP3A and CYP2C8 for dosing instructions and monitor for lack of efficacy of the concomitant treatment; **avoid** combined hormonal contraceptives, implants, and progestin-only pills
	repaglinide	CYP2C8	0.65	
repotrectinib	midazolam	**CYP3A**	**0.31**	**avoid** CYP3A substrates where minimal concentration changes can cause reduced efficacy; if unavoidable, adjust the CYP3A substrate dosage according to the prescribing information; avoid hormonal contraceptives and advise female patients to use an effective nonhormonal contraceptive
sotagliflozin	midazolam	CYP3A	0.79	none
sparsentan	bupropion	CYP2B6	0.67	**monitor** for efficacy of CYP2B6 substrates and consider dose adjustment in accordance with the prescribing information of these drugs

Table 4. Transporter-mediated DDIs, NMEs as substrates

NME	Inhibitor	Transporter	AUCR	Label Recommendation
iptacopan	cyclosporine	P-gp, BCRP, OATP1B1, OATP1B3	1.50	none
momelotinib	rifampin[1]	OATP1B1, OATP1B3	1.57	**monitor** for adverse reactions
zavegepant	rifampin[1]	**OATP1B3, NTCP**	**2.39[2]**	**avoid** inhibitors of OATP1B3 or NTCP

[1] single dose; [2] based on PBPK modeling and simulations

Table 5. Transporter-mediated DDIs, NMEs as inhibitors

NME	Substrates	Transporter	AUCR	Label Recommendation
elacestrant	digoxin	P-gp	1.13	reduce the dosage of P-gp and BCRP substrates when minimal concentration changes may lead to serious or life-threatening adverse reactions
	rosuvastatin	BCRP	1.23	
momelotinib	rosuvastatin	**BCRP**	**2.73**	initiate rosuvastatin at 5 mg and do not increase to more than 10 mg once daily; dose adjustment with other BCRP substrates may also be needed as per their approved prescribing information
nirmatrelvir and ritonavir	dabigatran	P-gp	1.94	**caution** for digoxin with appropriate monitoring of serum digoxin levels; refer to the digoxin product label for further information
pirtobrutinib	digoxin	P-gp	1.35	concomitant use of P-gp or BCRP substrates may increase the risk of adverse events related to these substrates for drugs which are sensitive to minimal concentration changes; follow recommendations for P-gp and BCRP substrates provided in their approved product labeling
	rosuvastatin	**BCRP**	**2.40**	
ritlecitinib	sumatriptan	OCT1	1.50	none
sotagliflozin	digoxin	P-gp	1.31	**monitor** digoxin levels
sparsentan	pitavastatin	P-gp, BCRP, OATP1B1, OATP1B3, OATP2B1, and NTCP	0.70	**avoid** sensitive P-gp and BCRP substrates