RISK OF PHARMACOKINETIC DRUG-DRUG INTERACTIONS WITH NOVEL DRUGS APPROVED BY THE US FDA IN 2022: A DETAILED REVIEW OF DDI DATA FROM NDA DOCUMENTATION

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Abstract

Understanding the ADME processes involved in pharmacokinetic-based drug-drug interactions (DDIs) is critical to facilitate an optimal management of DDIs in the clinic. In the present work, drug metabolism and transport *in vitro* and *in vivo* data for small molecular drugs approved by the U.S. Food and Drug Administration in 2022 (N = 22) were analyzed using the Certara Drug Interaction Database (https://www.druginteractionsolutions.org/). The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the new drug application (NDA) reviews. When considered as victim drugs, 17 drugs showed some level of metabolism *in vitro*, and *in vivo* 10 were identified to be clinical substrates based on DDI studies with enzyme inhibitors and/or pharmacogenetic evaluations. Among them, 7 drugs were substrates of CYP3A, and daridorexant and mitapivat were found to be sensitive substrates with predicted AUCRs of 5.90 and 5.00, respectively, when co-administered with the strong CYP3A index inhibitor itraconazole. Five drugs were sensitive to CYP3A induction, namely adagrasib, lenacapavir, mitapivat, olutasidenib, and vonoprazam, with AUCRs of 0.05-0.20 when co-administered with rifampin, a strong CYP3A index inducer. As inhibitors, 12 drugs and 4 metabolites showed positive inhibition *in vitro*. *In vivo*, only 3 of them were confirmed to be clinical inhibitors of CYP enzymes based clinical and/or PBPK results with marker substrates: adagrasib (strong CYP3A and moderate CYP2C9 and CYP2D6 inhibitor), lenacapavir (moderate CYP3A inhibitor), and vonoprazan (weak CYP2C19 and CYP3A inhibitor). As inducers, 12 drugs and 6 metabolites showed positive results *in vitro*, while *in vivo* only 2 drugs showed weak-to-moderate induction: mavacamten (CYP2C8/CYP2C9/CYP2C19/CYP3A) and mitapivat (CYP3A). Regarding transporter data, 8 drugs and 6 metabolites were substrates of transporters *in vitro*, while *in vivo* no clinical sensitive or moderate sensitive substrates were identified. Only 2 drugs were found to be weak substrates, including abrocitinib (OAT3) and deucravacitinib (P-gp/BCRP), with an AUCR of 1.66 and 1.29, respectively, when co-administered with probenecid and cyclosporine. As inhibitors, 16 drugs and 7 metabolites showed positive *in vitro* results. Based on clinical and physiologically-based pharmacokinetic (PBPK) data, 4 drugs (abrocitinib, adagrasib, lenacapavir, and oteseconazole) were found to inhibit P-gp (highest AUCR = 1.53, dabigatran) and 3 of them also inhibited BCRP (highest AUCR = 2.14, rosuvastatin). As expected, all DDIs with AUC changes ≥ 2-fold triggered dosing recommendations in the drugs' labels. Some DDIs with an AUC change < 2 also had label recommendations likely pertaining to concomitant use of drugs with a narrow therapeutic index (e.g., futibatinib, mavacamten, and pacritinib as CYP3A substrates; vonoprazan as a CYP2C19 inhibitor; mavacamten as a CYP3A inducer; abrocitinib, adagrasib, and lenacapavir as P-gp inhibitors). Overall, CYP3A continued to play a major role in the drug disposition of the 2022 drugs, mediating all strong drug interactions.

Objectives

- To review *in vitro* and pharmacokinetic-based clinical DDI data available in the NDA reviews for drugs approved by the FDA in 2022
- 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 all small new molecular entities (NMEs) approved (N = 22), 17 drugs showed some level of metabolism *in vitro.*
- *In vivo,* 10 drugs were identified to be clinical substrates based on DDIs studies with inhibitors and/or pharmacogenetic evaluations, including 4 drugs identified based on PBPK data (**Table 1**).
- All CYP3A substrates (N = 8) were sensitive to induction, with AUCRs 0.05-0.36 when co-administrated with rifampin, a strong index CYP3A inducer. Four drugs were evaluated using PBPK modeling and simulations.
- As inhibitors, 12 drugs and 4 metabolites showed positive inhibition *in vitro*. *In vivo*, only 3 of them were confirmed to be clinical inhibitors of CYPs (**Table 2**).
- As inducers, 12 drugs and 6 metabolites showed positive results *in vitro*, while *in vivo* only 2 drugs showed weak-to-moderate induction based on PBPK modeling and simulations (**Table 3**).

Transporter-mediated DDIs

- 8 drugs and 6 metabolites were substrates of transporters *in vitro*, while *in vivo* only 2 drugs were found to be weak substrates (**Table 4**).
- 4 drugs were found to be clinical inhibitors of P-gp or BCRP (**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

NMEs	Therapeutic Class	Inhibitor	Enzyme	AUCR	Label Recommendation
abrocitinib*	Antineoplastic Agents	fluconazole	CYP2C19, CYP2C9	4.85	**avoid** moderate to strong inhibitors of both CYP2C19 and CYP2C9
adagrasib*	Antineoplastic Agents	itraconazole	CYP3A	3.97	**avoid** strong CYP3A inhibitors until adagrasib concentrations have reached steady state
daridorexant	Nervous System	itraconazole	CYP3A	5.90 (PBPK)	**avoid** strong CYP3A inhibitors
deucravacitinib	Immunosuppressants	fluvoxamine	CYP1A2	1.57; 1.22 (active moiety)	none
futibatinib*	Antineoplastic Agents	itraconazole	CYP3A	1.41	**avoid** dual P-gp and strong CYP3A inhibitors
lenacapavir*	Antivirals	Atazanavir/ cobicistat	CYP3A, UGT1A1	4.21	**not recommended** with combined P-gp, UGT1A1, and strong CYP3A inhibitors
mavacamten	Cardiovascular Drugs	fluconazole	CYP2C19	3.10 (CYP2C19 NMs; PBPK)	**contraindicated** with strong CYP2C19 inhibitors
		itraconazole	CYP3A	1.29 (CYP2C19 NMs; PBPK)	**contraindicated** with strong CYP3A inhibitors
mitapivat*	Hematological Agents	itraconazole	CYP3A	5.00 (PBPK)	**avoid** strong CYP3A inhibitors
pacritinib	Antineoplastic Agents	clarithromycin	CYP3A	1.82	**contraindicated** with strong CYP3A inhibitors
vonoprazan	Gastrointestinal Agents	ketoconazole	CYP3A	1.73 (CYP2D6 NMs; PBPK)	none
		ketoconazole	CYP3A, CYP2D6	2.53 (CYP2D6 PMs; PBPK)	none
		NA	CYP2C19	1.50 (CYP2C19 PMs vs. NMs)	none

* P-gp substrate *in vitro*; NM, normal metabolizer; PM, poor metabolizer

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- CYP3A was found to play a major role in the drug disposition of drugs approved in 2022, mediating all strong drug interactions.
- PBPK was commonly used to evaluate enzyme-mediated DDIs with new drugs as substrates (40%), inhibitors (30%), and inducers (100%).
- All transporter-mediated DDIs led to AUCRs below (or close to) 2-fold.

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Additional Results

Table 2. Enzyme-mediated DDIs, NMEs as inhibitors

NME	Substrate	AUCR	Enzyme	Label Recommendation
adagrasib	midazolam	31.40 (PBPK)	CYP3A	**avoid** sensitive CYP3A substrates
	(S)-warfarin	2.93 (PBPK)	CYP2C9	**avoid** sensitive CYP2C9 where minimal concentration changes may lead to serious adverse reactions
	dextromethorphan	2.37 (PBPK)	CYP2D6	**avoid** sensitive CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions
lenacapavir	midazolam	4.08	CYP3A	use with **caution** for midazolam; refer to the prescribing information of the sensitive CYP3A substrate dosing recommendations with moderate inhibitors of CYP3A
vonoprazan	midazolam	1.89	CYP3A	none
	proguanil	1.42	CYP2C19	carefully **monitor** the efficacy or adverse reactions associated with CYP2C19 substrates and refer to the prescribing information for dosage adjustments or consider alternative

Table 3. Enzyme-mediated DDIs, NMEs as Inducers

NME	Substrate	AUCR	Enzyme	Label Recommendation
mavacamten	midazolam	0.55 (CYP2C19 NMs; PBPK)	CYP3A	Closely **monitor** when used in combination with CYP3A, CYP2C19, or CYP2C9 substrates where decreases in the plasma concentration of these drugs may reduce their activity
	omeprazole	0.33* (CYP2C19 PMs; PBPK)	CYP2C19	
	tolbutamide	0.46 (CYP2C19 NMs; PBPK)	CYP2C9	
	repaglinide	0.73 (CYP2C19 NMs; PBPK)	CYP2C8	none
mitapivat	midazolam	0.43 (PBPK)	CYP3A	**monitor** for loss of therapeutic effect of sensitive CYP3A substrates with narrow therapeutic index when co-administered

*the confidence in the predicted effects in NMs is low due to limitations in the model, and data is not shown in the NDA review; NM, normal metabolizer; PM, poor metabolizer

Table 4. Transporter-mediated DDIs, NMEs as substrates

NME	Inhibitor	AUCR	Transporter	Label Recommendation
abrocitinib	probenecid	1.66	OAT3	none
deucravacitinib	cyclosporine	1.29	P-gp, BCRP	none

Table 5. Transporter-mediated DDIs, NMEs as inhibitors

NME	Substrate	AUCR	Transporter	Label Recommendation
abrocitinib	dabigatran etexilate	1.53	P-gp	**monitor or titrate dosage of P-gp substrate** where small concentration changes may lead to serious or life-threatening toxicities
adagrasib	digoxin	1.48 (PBPK)	P-gp	**avoid P-gp substrates** where minimal concentration changes may lead to serious adverse events unless otherwise recommended in the Prescribing Information for these substrates; adagrasib is **a P-gp inhibitor**, concomitant use increases exposure of P-gp substrates, which may increase the risk of adverse reactions related to these substrates
	rosuvastatin	1.35	BCRP	none
lenacapavir	tenofovir alafenamide fumarate	1.32; 1.47 (tenofovir)	P-gp	use with **caution** with **digoxin** and monitor digoxin therapeutic concentrations; refer to the **direct acting anticoagulants** prescribing information for concomitant administration with **combined moderate CYP3A and P-gp inhibitors**; lenacapavir is **a P-gp inhibitor**
	rosuvastatin	1.31	BCRP	none (but indicated that lenacapavir is a BCRP inhibitor)
oteseconazole	rosuvastatin	2.14	BCRP	concomitant use with BCRP substrates may increase the exposure of drugs that are BCRP substrates, which may increase the risk of adverse reactions associated with these drugs; **use the lowest possible starting dose of the BCRP substrate** or consider **reducing the dos**e of the substrate drugs and **monitor for adverse reactions**