Detailed Evaluation of Pharmacokinetic-based Drug-drug Interaction Data Contained in New Drug and Biologic License Applications of Drugs Approved by the U.S. FDA in 2015

Jingjing Yu[1], Zhu Zhou[2], Katie Owens[1], Tasha K. Ritchie[1], and Isabelle Ragueneau-Majlessi[1]

[1]Drug Interaction Database Program, Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle WA 98105; [2]Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA 95211

SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON
Drug Interaction Database Program

BACKGROUND

The aim of the present work was to perform a systematic analysis of metabolism, transport, and drug interaction data available in New Drug Applications (NDAs) and Biologic License Applications (BLAs) of drugs approved in 2015, and highlight significant findings.

METHODS

Using the University of Washington Metabolism and Transport Drug Interaction Database® (DIDB) (http://www.druginteractioninfo.org/), all drug metabolism, transport, pharmacokinetic (PK), and drug-drug interaction (DDI) data available in the regulatory documentation were analyzed. All the NDA and BLA Reviews and Product Labels of these New Molecular Entities (NMEs) were obtained from Drugs@FDA.

RESULTS

- Thirty three NDAs and 12 BLAs were approved in 2015. All of the NDAs and five BLAs had pre-clinical and/or clinical DDI data available and were fully analyzed (a total of 38 NMEs).
- Consistent with the 2012 FDA DDI Draft guidance, a majority of the NMEs were evaluated *in vitro* as substrates and inhibitors/inducers of drug-metabolizing enzymes and transporters.
- Overall, 95 positive *in vivo* DDI studies (AUC ratio ≥ 1.25 for inhibition or ≤ 0.8 for induction) were observed and involved 21 NMEs (64%), with the NMEs being mainly victim drugs. Clinical DDIs yielding an AUC ratio of ≥ 2 (for inhibition) or ≤ 0.5 (for induction) are presented in Tables 1-3, as a 2-fold change in drug exposure often triggers dosing recommendations.

Clinically significant DDIs: considering both metabolism and transport-mediated interactions

Table 1: Significant inhibition with max AUC or C_{max} ratio ≥ 2, NMEs as substrates (n = 13)

Substrate	Perpetrator	Max AUC Ratio	Max C_{max} Ratio	Enzyme/ Transporter Possibly Affected	Labeling Impact	Brand Name
Ivabradine	Ketoconazole	7.70	3.60	CYP3A, P-gp	Contraindication	CORLANOR
Cobimetinib	Itraconazole	6.70	3.20	CYP3A, P-gp	Avoid	COTELLIC
Flibanserin	Fluconazole	6.41	2.11	CYP3A, CYP2C19 (minor), CYP2C9 (minimal)	Contraindication	ADDYI
	Ketoconazole	4.61	1.84	CYP3A (CYP2C8/9 minimal)		
Isavuconazonium sulfate	Ketoconazole	5.22	1.09	CYP3A	Contraindication	CRESEMBA
Eluxadoline	Cyclosporine	4.20	6.80	OATP1B1, (MRP2/P-gp minimal)	Avoid or reduce dose	VIBERZI
Cariprazine	Ketoconazole	3.78	3.26	CYP3A	Reduce dose	VRAYLAR
Daclatasvir	Ketoconazole	3.00	1.57	CYP3A, CYP2C8 (minor), P-gp	Reduce dose	DAKLINZA
Tenofovir alafenamide fumarate	Cobicistat	2.65	2.80	P-gp, BCRP, OATP1B1/3	None	GENVOYA
Sonidegib	Ketoconazole	2.26	1.50	CYP3A	Avoid	ODOMZO
Daclatasvir	Simeprevir	2.20	1.60	CYP3A, P-gp	Reduce dose	DAKLINZA
	Ketoconazole	2.17	1.18	CYP3A	Reduce dose	REXULTI
Brexpiprazole	Quinidine	2.03 (EMs)	1.12 (EMs)	CYP2D6	Reduce dose	REXULTI
Selexipag	Lopinavir/ritonavir	2.00	2.00	P-gp, OATP1B1/3	None	UPTRAVI

Table 2: Significant induction with max AUC or C_{max} ratio ≤ 0.5, NMEs as substrates (n = 15)

Substrate	Perpetrator	Max AUC Ratio	Max C_{max} Ratio	Enzyme/ Transporter Possibly Affected	Labeling Impact	Brand Name
Isavuconazonium sulfate	Rifampin	0.03	0.25	CYP3A	Contraindication	CRESEMBA
Flibanserin	Rifampin	0.04	0.09	CYP3A, CYP2C19 (minor), CYP2C8/9 (minimal)	Not recommend	ADDYI
Rolapitant	Rifampin	0.12	0.68	CYP3A	Avoid	VARUBI
Palbociclib	Rifampin	0.15	0.28	CYP3A, P-gp	Avoid	IBRANCE
Cobimetinib	Rifampin	0.17 (PBPK)	0.37 (PBPK)	CYP3A, P-gp	Avoid	COTELLIC
Daclatasvir	Rifampin	0.21	0.44	CYP3A, CYP2C8 (minor), P-gp	Contraindication	DAKLINZA
Brexpiprazole	Rifampin	0.24	0.69	CYP3A	Double dose 1-2 weeks	REXULTI
Alectinib	Rifampin	0.27 (M4 1.80; A+M4 0.82)	0.49 (M4 2.20; A+M4 0.96)	CYP3A, P-gp	None	ALECENSA
Sonidegib	Rifampin	0.28	0.46	CYP3A	Avoid	ODOMZO
Panobinostat	Rifampin	0.30 (PBPK)	0.40 (PBPK)	CYP3A, P-gp	Avoid	FARYDAK
Ivabradine	St. John's Wort extract	0.40-0.50	0.70-0.80	CYP3A, P-gp	Avoid	CORLANOR
Ixazomib citrate	Rifampin	0.46	0.26	CYP3A, P-gp (minor)	Avoid	NINLARO

Table 3: Significant DDIs (max AUC or C_{max} ratio ≥ 2 or ≤ 0.5, NMEs as inhibitors or inducers (n = 4)

Perpetrator	Substrate	Max AUC Ratio	Max C_{max} Ratio	Enzyme/ Transporter Possibly Affected	Labeling Impact	Brand Name
Rolapitant	Dextromethorphan	2.77	3.33	CYP2D6	Contraindicate or avoid with NTR CYP2D6 substrate	VARUBI
	Sulfasalazine	2.18	2.38	BCRP	Monitor NTR BCRP substrate	
Isavuconazonium sulfate	Tacrolimus	2.25	1.42	CYP3A	Caution, monitor drug exposure and adverse event, dose adjustment	CRESEMBA
Panobinostat	Dextromethorphan	1.20-2.30	1.20-3.00	CYP2D6	Avoid sensitive or NTR CYP2D6 substrate	FARYDAK
Lumacaftor	Ivacaftor	0.20	Not available	CYP3A	Not recommend with sensitive or NTR CYP3A substrate	ORKAMBI

Notes for Tables 1-3: Potent inhibitor (AUC ratio ≥ 5) and inducers (AUC ratio ≤ 0.2) are highlighted in red; NTR, narrow therapeutic range; EM, extensive metabolizer.

DDI evaluations through PBPK simulation and modeling

Seven NDAs included PBPK simulations: alectinib, aripiprazole lauroxil, cobimetinib, lenvatinib, osimertinib, panobinostat, and sonidegib; three with positive PBPK results were used to guide labeling recommendations and presented in Table 4.

Table 4: DDI findings through PBPK (n = 3)

Substrate	Inhibitor / AUC Ratio	Inducer / AUC Ratio
Cobimetinib (COTELLIC)	Itraconazole (strong CYP3A inhibitor) / 6.7 Erythromycin (moderate CYP3A inhibitor) / 3.0 Diltiazem (moderate CYP3A inhibitor) / 4.0 Fluvoxamine (weak CYP3A inhibitor) / 1.0	Rifampin (strong CYP3A inducer) / 0.17 Efavirenz (moderate CYP3A inducer) / 0.27
Panobinostat (FARYDAK)	Ketoconazole (strong CYP3A inhibitor) / 1.7	Rifampin (strong CYP3A inducer) / 0.30
Sonidegib (ODOMZO)	Ketoconazole (strong CYP3A inhibitor) / 2.3 Erythromycin (moderate CYP3A inhibitor) / 1.8-2.8	Rifampin (strong CYP3A inducer) / 0.28 Efavirenz (moderate CYP3A inducer) / 0.31-0.44

Notes: DDIs in black - evaluated through clinical studies; DDIs in blue - evaluated through PBPK.

Pharmacogenetic (PGx) studies

Eight NMEs presented some PGx data related to drug metabolism and transport: brexpiprazole (CYP2D6), cariprazine (CYP2D6), edoxaban (CYP2C9, VKORC1, P-gp), eluxadoline (OATP1B1), flibanserin (CYP2C9, 2C19, 2D6), lenvatinib (CYP1A2, 2A6, 2C19, 3A5), lesinurad (CYP2C9), panobinostat (CYP3A5), and trabectedin (CYP3A4); three showed positive results and the PGx results were used in their dose recommendations (Table 5).

Table 5: PGx findings (n = 3)

Substrate	Enzyme	Perpetrator	AUC Ratio	C_{max} Ratio	Population Studied	Labeling Impact
Brexpiprazole (ZYDELIG)	CYP2D6 , CYP3A	EM/PM study	1.76	1.15	CYP2D6 PMs vs. (EMs and IMs)	Half dose
		Quinidine	2.03	1.12	CYP2D6 EMs and IMs	Half dose
		Ketoconazole	2.17	1.18	CYP2D6 EMs and IMs	
		Strong CYP3A4 inhibitors	4.8 (popPK)	Not available	CYP2D6 PMs	Quarter dose
		Strong CYP2D6 and 3A4 inhibitors	5.1 (popPK)	Not available	CYP2D6 EMs	
Flibanserin (ADDYI)	CYP2C19	EM/PM study	1.34	1.49	CYP2C19 PMs vs. EMs	Caution with PMs and CYP2C19 inhibitors
Lesinurad (AKYNZEO)	CYP2C9	EM/PM study	2.11	1.75	CYP2C9 PMs vs. EMs	Caution with PMs

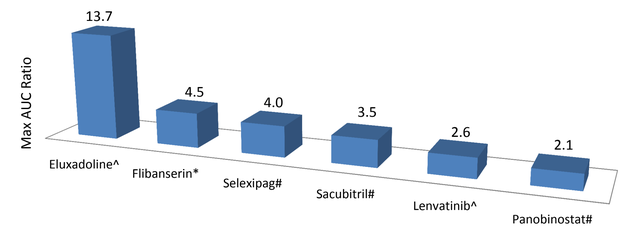
Notes: IM, intermediate metabolizer; PM, poor metabolizer.

Organ impairment studies

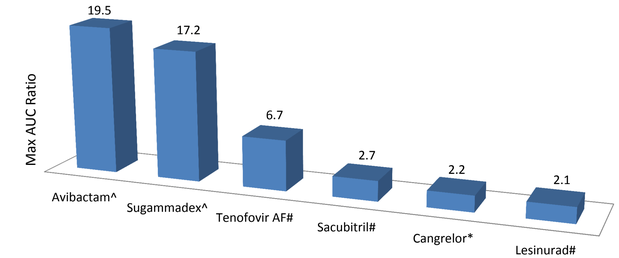
- Twenty five NMEs were evaluated for the impact of hepatic (HI) and/or renal impairment (RI) on drug exposure. Twelve and nine drugs had an AUC ratio (impaired/control) ≥ 1.25 in HI and RI patients, respectively, resulting in dosing recommendations.
- Four and one NMEs had AUC ratios < 1.25 in HI and RI patients, respectively, however dosing recommendations were still advised in the labeling. All the study results with AUC ratio ≥ 2 are presented in Figures 1A (HI) and 1B (RI).

Figure 1: Hepatic and renal impairment study results with AUC ratios ≥ 2 (n = 6 for HI; n = 6 for RI)

A.



B.



Notes: *RI CLcr 20-70 mL/min; #Severe RI CLcr < 30 mL/min; ^ESRD, End Stage Renal Disease;
Tenofovir AF: a prodrug, tenofovir was measured, a fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate; Sacubitril, a prodrug, active metabolite LBQ657 was measured.

CONCLUSIONS

- Forty five NMEs were approved by the FDA in 2015, including 33 NDAs.
- As substrates, five NMEs were considered sensitive substrates of CYP3A based on the FDA classification, with changes in exposure ≥ 5-fold.
- As perpetrators, most clinically significant DDIs were weak-to-moderate inhibition and induction, with only one NME, lumacaftor (in combination with ivacaftor) considered as a strong inducer of CYP3A, whereas none showed strong inhibition.
- In addition to clinical DDI studies, PBPK simulations and PGx studies were used for seven and eight NMEs, respectively, to inform dosing recommendations. The effects of hepatic and renal impairment on the drugs' PK were also evaluated to support drug administration in these specific populations.

References

- Yu J, Zhou Z, Owens KH, Ritchie TK, Ragueneau-Majlessi I. What Can Be Learned from Recent New Drug Applications? A Systematic Review of Drug Interaction Data for Drugs Approved by the U.S. FDA in 2015, *Drug Metabolism and Disposition*, 2017 Jan; 45(1):86-108.
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- Drugs@FDA http://www.accessdata.fda.gov/scripts/cder/daf/