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BRIEF REPORT

In Vitro-to-*In Vivo* Extrapolation of Transporter Inhibition Data for Drugs Approved by the US Food and Drug Administration in 2018

Jingjing Yu[1,*] and Isabelle Ragueneau-Majlessi[1]

A systematic analysis of the inhibition transporter data available in New Drug Applications of drugs approved by the US Food and Drug Administration (FDA) in 2018 (*N* = 42) was performed. *In vitro*-to-*in vivo* predictions using basic models were available for the nine transporters currently recommended for evaluation. Overall, 29 parents and 16 metabolites showed *in vitro* inhibition of at least one transporter, with the largest number of drugs found to be inhibitors of P-gp followed by BCRP. The most represented therapeutic areas were oncology drugs and anti-infective agents, each comprising 31%. Among drugs with prediction values greater than the FDA recommended cutoffs and further evaluated *in vivo*, 56% showed positive clinical interactions (area under the concentration-time curve ratio (AUCRs) ≥ 1.25). Although all the observed or simulated inhibitions were weak (AUCRs < 2), seven of the nine interactions (involving five drugs) resulted in labeling recommendations. Interestingly, more than half of the drugs with predictions greater than the cutoffs had no further evaluations, highlighting that current basic models represent a useful, simple first step to evaluate the clinical relevance of *in vitro* findings, but that multiple other factors are considered when deciding the need for clinical studies. Four drugs had prediction values less than the cutoffs but had clinical evaluations or physiologically-based pharmacokinetic simulations available. Consistent with the predictions, all of them were confirmed not to inhibit these transporters *in vivo* (AUCRs of 0.94–1.09). Overall, based on the clinical evaluations available, drugs approved in 2018 were found to have a relatively limited impact on drug transporters, with all victim AUCRs < 2.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Following the US Food and Drug Administration (FDA) drug interaction guidance, the potential for drugs to inhibit transporters should be evaluated using a mechanistic approach, and clinical studies should be considered based on the risk with likely comedications.

WHAT QUESTION DID THE STUDY ADDRESS?

☑ Through a systematic review of transporter-based inhibition data for drugs approved by the FDA in 2018, this report provides an in-depth analysis on how *in vitro* results were used to predict the drug-drug interaction risk and guide necessary clinical assessments.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Although current basic models represent a useful, simple first step to evaluate the clinical relevance of *in vitro* findings, multiple other factors are considered when deciding the need for further clinical evaluations. The results of the available clinical evaluations show that drugs approved in 2018 have a relatively limited risk of significant transporter-based interactions.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The present work provides an in-depth analysis of the most recent examples of *in vitro*-to-*in vivo* extrapolation for transporter inhibition.

The evaluation of the risk of transporter-based drug interactions is now an integral part of the drug development process, supporting the safe use of new treatments in the intended patient populations.[1] A systematic, risk-based, integrated approach, including *in vitro*, *in silico*, and *in vivo* evaluations, has been recommended to evaluate transporter-mediated drug-drug interactions (DDIs) and recently has been updated by several regulatory agencies.[2–5] As a perpetrator, in general, a new drug should be evaluated *in vitro* for its potential to inhibit the following transporters, which have been shown to play a major role in drug disposition and interact with drugs in clinical use: P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), Organic Anion Transporting Polypeptide 1B1 (OATP1B1), OATP1B3, Organic Anion Transporter 1 (OAT1), OAT3, Organic Cation Transporter 2 (OCT2), Multidrug and Toxin Extrusion protein

[1]Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, Washington, USA. *Correspondence: Jingjing Yu (jingyu@uw.edu)
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1 (MATE1), and MATE2-K. Then following *in vitro*-to-*in vivo* model-based prediction using basic and/or mechanistic models like physiologically-based pharmacokinetic (PBPK) models, further clinical evaluations (drug interaction studies or *in silico* predictions) may be warranted based on likely concomitant medications that are known transporter substrates in the indicated patient populations. This report provides a summary of transporter-based inhibition data available in the 2018 US Food and Drug Administration (FDA) New Drug Applications (NDAs) and describes whether *in vitro* results are used to predict the risk of drug interactions and guide necessary clinical assessments.

METHODS

This analysis was performed using the University of Washington Drug Interaction Database that contains manually curated *in vitro* and clinical drug interaction data from NDA reviews and the literature (http://www.druginteractioninfo.org). All transporter-based *in vitro* and *in vivo* pharmacokinetic (PK) drug interaction data evaluating new drugs and their metabolites as inhibitors were examined. Using the basic models recommended in the most recent FDA DDI guidance (2017),[2] prediction values for each transporter were calculated using *in vitro* inhibition and clinical PK information. DDI study results were generally obtained from dedicated clinical trials but also, in some cases, from PBPK modeling and simulations, which are increasingly accepted in lieu of clinical trials to guide dosing recommendations. Following the methodology previously described,[6] mean area under the plasma drug concentration-time curve ratios (AUCRs) were used to categorize clinical interactions, which was calculated based on the mean AUC values curated from the NDA reviews, with a positive study defined as an AUCR ≥ 1.25.

RESULTS

A total of 42 NDAs (representing 42 small new molecular entities) were approved by the FDA in 2018. Among them, 39 parent drugs and 23 metabolites (including the active moieties of three prodrugs) were evaluated *in vitro* as inhibitors of transporters. A total of 13 transporters were evaluated. In addition to the regulatory recommended transporters, bile salt export pump, multidrug resistance-associated protein 2, OAT2, and OCT1 were also studied. Overall, 29 parents and 16 metabolites showed *in vitro* inhibition of at least one transporter, defined by at least 20% inhibition observed at the highest test concentrations (**Figure 1**). The largest number of new molecular entities was found to be inhibitors of P-gp and BCRP. Among the 29 parent drugs, the most represented therapeutic areas were oncology drugs and anti-infective agents, each comprising 31% (**Figure 1**). Inhibition results with the FDA recommended transporters are discussed in detail in the following sections.

Efflux transporters P-gp and BCRP

A total of 35 parent drugs and 20 metabolites were evaluated for their potential to inhibit P-gp and BCRP *in vitro*.

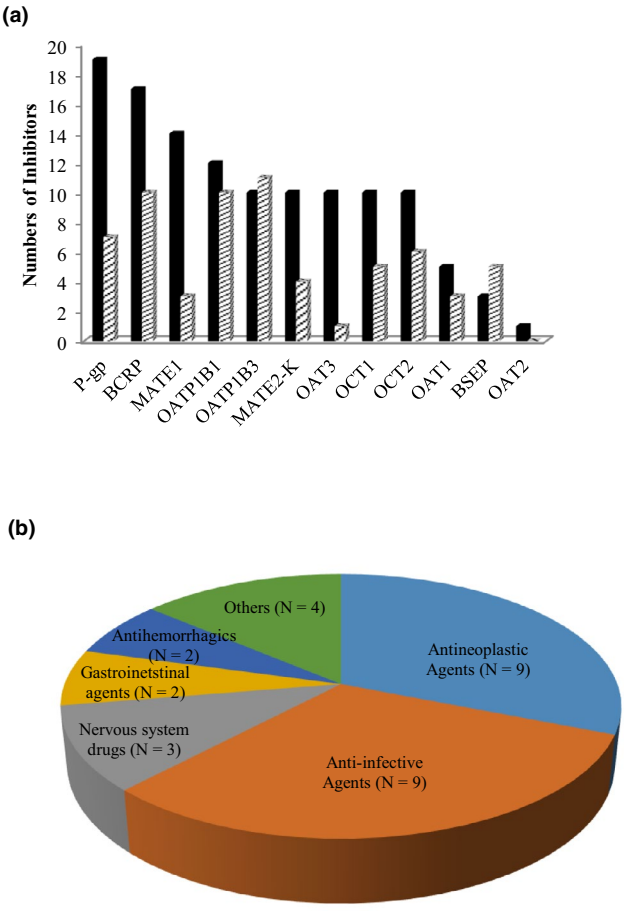

Figure 1 Numbers of new molecular entities (NMEs; black bars) and metabolites (striped bars) that are inhibitors of transporters *in vitro* (**a**) and therapeutic classes of these inhibitors (*N* = 29) (**b**). Numbers of drugs in each therapeutic class are presented in parentheses. Others include four therapeutic classes, namely alimentary tract and metabolism products (*N* = 1), immunosuppressants (*N* = 1), respiratory system products (*N* = 1), and treatment of pain and inflammation (*N* = 1).

Using the basic model, I_{gut}/half-maximal inhibitory concentration (IC_{50}) ratios were calculated for the inhibitors of P-gp (*N* = 19) and BCRP (*N* = 17; **Figure 1**), where I_{gut} is the dose of inhibitor/250 mL. Drugs and active metabolites of prodrugs with I_{gut}/IC_{50} ratios ≥ 10 (FDA cutoff) are presented in **Table 1**. Other metabolites and prodrugs with inhibition of the same transporter are also listed regardless of the prediction values. For the P-gp inhibitors with a prediction value over 10 (*N* = 13), only 5 (38%) were further evaluated in clinical studies (using digoxin as the marker substrate), and 4 drugs (elagolix, fostamatinib, sarecycline, and tezacaftor/ivacaftor) showed small but significant increases in digoxin exposure (26–37% increase in AUC and 33–71% increase in C_{max}). Based on these observations, it is recommended to monitor the potential toxicity of co-administered P-gp substrates as they might require dose reduction.[7–10] Similarly, among the 12 BCRP inhibitors with I_{gut}/IC_{50} ratios ≥ 10, just 3 (25%) were further evaluated clinically, using the clinical substrate rosuvastatin.

Table 1 Drugs approved by the FDA in 2018 that have prediction values greater than the FDA cutoffs[2]

Drug name	Therapeutic class	IC_{50} (μM)	Prediction value[a]	Clinical substrate	AUCR	$C_{max}R$	Labeling recommendation
P-gp inhibitors (*N* = 13)							
Baloxavir marboxil[b]	Anti-infective agents	8.75[c]	64	Digoxin	0.86	1.00	None
Baloxavir[d]		37.3% at 20.9 μM	< 10				
Dacomitinib	Antineoplastic agents	N/A	> 10	N/T	N/T	N/T	None
Doravirine	Anti-infective agents	N/A	> 10	N/T	N/T	N/T	None
Elagolix	Treatment of pain and inflammation	54	23	Digoxin	1.26	1.71	May increase plasma concentrations of drugs that are substrates of P-gp
Encorafenib	Antineoplastic agents	> 50	21	N/T	N/T	N/T	None
Fostamatinib[b]	Antihemorrhagics	3.2	323	Digoxin	1.37	1.65	Monitor for toxicities of P-gp substrate drugs that may require dosage reduction
Glasdenib	Antineoplastic agents	> 33	104	N/T	N/T	N/T	None
Ivosidenib	Antineoplastic agents	19.6	175	N/T	N/T	N/T	None
Lorlatinib	Antineoplastic agents	2.99	329	N/T	N/T	N/T	None
Rifamycin	Anti-infective agents	6.5	342	N/T	N/T	N/T	None
Sarecycline	Anti-infective agents	6.95	177	Digoxin	1.03	1.26	Monitor for toxicities of drugs that are P-gp substrates and may require dose reduction
Stiripentol	Nervous system drugs	92.1	695	N/T	N/T	N/T	Considering reducing dose of P-gp substrates of P-gp if adverse reactions are experienced
Tezacaftor/ivacaftor[e]	Respiratory system products	28.6	27	Digoxin	1.30	1.33	Caution and appropriate monitoring should be used with digoxin or other P-gp substrates with an NTR
BCRP inhibitors (*N* = 12)							
Avatrombopag	Antihemorrhagics	5.4	68	N/T	N/T	N/T	None
Baloxavir marboxil[b]	Anti-infective agents	48.3% at 78.1 μM	< 10	Rosuvastatin	0.83	0.82	None
Baloxavir[d]		7.10[c]	79				
Dacomitinib	Antineoplastic agents	N/A	> 10	N/T	N/T	N/T	None
Doravirine	Antineoplastic agents	51	18	N/T	N/T	N/T	None
Encorafenib	Antineoplastic agents	10	333	N/T	N/T	N/T	None
M42.5[d]		N/A					
Fostamatinib[b]	Antihemorrhagics	0.05	20,673	Rosuvastatin	1.96	1.88	Monitor for toxicities of BCRP substrate drugs that may require dosage reduction
R406[d]		0.031	33,344				
Gilteritinib	Antineoplastic agents	1.4	620	N/T	N/T	N/T	None
Glasdegib	Antineoplastic agents	4.6	232	N/T	N/T	N/T	None
Lorlatinib	Antineoplastic agents	> 94.9	10.4	N/T	N/T	N/T	None
Rifamycin	Anti-infective agents	> 34.4	65	N/T	N/T	N/T	None

(Continues)

Table 1 (Continued)

Drug name	Therapeutic class	IC_{50} (μM)	Prediction value[a]	Clinical substrate	AUCR	$C_{max}R$	Labeling recommendation
Stiripentol	Nervous system drugs	2.34	27,359	N/T	N/T	N/T	Consider reducing dose of BCRP substrates if adverse reactions are experienced
Tecovirimat	Anti-infective agents	6	1,063	N/T	N/T	N/T	None
OATP1B1/1B3 inhibitors (*N* = 3)							
Elagolix	Treatment of pain and inflammation	1.7 (OATP1B1); 4.7 (OATP1B3)	> 1.25	Rosuvastatin	0.88[f]; 0.59[g]	1.67[f]; 0.99[g]	Consider increasing the dose of rosuvastatin
Encorafenib	Antineoplastic agents	5.35 (OATP1B1); 6.16 (OATP1B3)	≥ 1.1	N/T	N/T	N/T	None
Ivosidenib	Antineoplastic agents	9.56 (OATP1B1); 22.8 (OATP1B3)	1.30	Rosuvastatin	1.04[h]	1.03[h]	None
OAT1/3 inhibitors (*N* = 4)							
Avatrombopag	Antihemorrhagics	0.2 (OAT3)	0.1	N/T	N/T	N/T	None
Encorafenib	Antineoplastic agents	4.2 (OAT1); 0.92 (OAT3)	0.23 (OAT1); 1.06 (OAT3)	N/T	N/T	N/T	None
Ivosidenib	Antineoplastic agents	0.322 (OAT3)	2.79	Methotrexate	1.36[h]	1.00[h]	None
Lorlatinib	Antineoplastic agents	2.72 (OAT3)	0.18	N/T	N/T	N/T	None
OCT2 inhibitors (*N* = 3)							
Bictegravir	Antineoplastic agents	0.42	0.311	Metformin	1.39	1.28	May increase plasma concentrations of OCT2 substrates; refer to metformin label for assessing the benefit and risk of concomitant use; contraindicate with dofetilide due to potential risk for serious and/or life-threatening events associated with dofetilide
Encorafenib	Antineoplastic agents	2.05[c]	0.48	N/T	N/T	N/T	None
Tafenoquine	Anti-infective agents	0.0419	0.16	N/T	N/T	N/T	Avoid OCT2 substrates; if not, monitor for drug-related toxicities and consider dose reduction of the co-administered drug
MATE1/2-K inhibitors (*N* = 7)							
Apalutamide	Antineoplastic agents	13.8 (MATE1)	0.04	Metformin	1.28[h]	N/A	None
M3[d]		17.6 (MATE1), 32% at 50 μM (MATE2-K)	N/A				
Bictegravir	Anti-infective agents	8.04 (MATE1)	0.02	Metformin	1.39	1.28	May increase plasma concentrations of MATE1 substrates; refer to metformin label for assessing the benefit and risk of concomitant use; contraindicate with dofetilide due to potential risk for serious and/or life-threatening events associated with dofetilide
Gilteritinib	Antineoplastic agents	0.054 (MATE1)	0.75	Cephalexin	0.98	0.91	None

(Continues)

Table 1 (Continued)

Drug name	Therapeutic class	IC_{50} (μM)	Prediction value[a]	Clinical substrate	AUCR	$C_{max}R$	Labeling recommendation
Glasdegib	Antineoplastic agents	4.9 (MATE1); 1.2 (MATE2-K)	0.06 (MATE1); 0.25 (MATE2-K)	N/T	N/T	N/T	None
Lorlatinib	Antineoplastic agents	3.71 (MATE1)	0.13 (MATE1)	N/T	N/T	N/T	None
Plazomicin	Anti-infective agents	2193 (MATE1); 570 (MATE2-K)	0.03 (MATE1); 0.11 (MATE2-K)	Metformin	1.04	1.04	None
Tafenoquine	Anti-infective agents	0.435[c] (MATE1); 0.170[c] (MATE2-K)	0.02 (MATE1); 0.04 (MATE2-K)	N/T	N/T	N/T	Avoid MATE substrates; if not, monitor for drug-related toxicities and consider dose reduction of the co-administered drug

AUCR, area under the concentration-time curve ratio; $C_{max}R$, C_{max} ratio; FDA, US Food and Drug Administration; IC_{50}, half-maximal inhibitory concentration; NTR, narrow therapeutic range; N/A, not available; N/T, not tested.

[a]The prediction values were calculated for all the drugs administered orally and their respective metabolites following the FDA drug-drug interaction guidance (2017), which was obtained from the New Drug Application reviews and double checked by the authors if the relevant data for the calculation were provided. I_{gut}/IC_{50} was calculated for P-gp and BCRP (cutoff ≥ 10; I_{gut} = dose of inhibitor/250 mL), $R = 1+ ((f_{u,p} \times I_{in,max})/IC_{50})$ for OATP1B1/3 (cutoff ≥ 1.1), and $C_{max,u}/IC_{50}$ for OAT1/3, OCT2, and MATE1/2-K (cutoff ≥ 0.1 for OAT and OCT and 0.02 for MATE). I_{gut} of parent drug was used for its active metabolite of the prodrug, assuming intermediate and complete conversion of parent drug to the active moiety in the gut lumen. Prediction values for metabolites were calculated using the metabolite concentrations when available. The lowest IC_{50} values were used if there were multiple values available or the IC_{50} values were estimated to be greater than the highest test concentrations. [b]Prodrug. [c]Unbound IC_{50} value. [d]Metabolite. [e]The inhibition was likely mainly caused by ivacaftor as clinical studies showed that ivacaftor alone resulted in a similar decrease in digoxin exposure. *In vitro*, ivacaftor also inhibited P-gp with an IC_{50} value of 0.17 μM. [f]Elagolix was administered as single dose. [g]Elagolix was administered as multiple doses. [h]Results were predicted using physiologically-based pharmacokinetic modeling and simulations.

Only fostamatinib was found to be a clinical inhibitor of BCRP (96% increase in AUC and 88% increase in C_{max} of rosuvastatin), triggering labeling recommendations to monitor co-administered BCRP substrates.[8] Of note, a transient 67% increase in the C_{max} of rosuvastatin was observed after a single dose administration of elagolix, however, rosuvastatin AUC was not significantly affected.[7] Interestingly, 9 of the 13 P-gp inhibitors were also BCRP inhibitors *in vitro*, indicating a significant overlap in substrate specificity between the two transporters, which is consistent with previous findings.[11] Overall, when both efflux transporters are considered, > 60% of the drugs with I_{gut}/IC_{50} ratios greater than the cutoff were not further evaluated *in vivo*, highlighting that the prediction ratio is only one component of the decision process for clinical evaluation, and that other factors are considered by sponsors and regulators in evaluating the need for a clinical study. For example, the I_{gut} value of doravirine was assuming complete dissolution of the clinical dose, whereas doravirine in the gut lumen is unlikely to reach the theoretical concentration based on the *in vitro* limited solubility, therefore, inhibition of intestinal P-gp and BCRP is unlikely to happen.[12] Additionally, a significant number of the drugs are indicated for cancer treatment and further clinical evaluations may not have been feasible in the indicated patient populations and difficult to perform in healthy subjects, explaining the lack of clinical information. One drug, stiripentol, has explicit labeling recommendations for P-gp and BCRP substrates based on *in vitro* findings, and a postmarketing requirement has been issued to conduct clinical DDI studies to evaluate the effect of stiripentol on the PK of sensitive substrates of the two transporters.[13]

Hepatic transporters OATP1B1 and OATP1B3

Based on the *in vitro* assays for 32 parent drugs, 12 were inhibitors of OATP1B1 and 10 of OATP1B3 (**Figure 1**), representing a total number of 13 drugs. Several drugs specifically inhibited one isoform (e.g., lorlatinib on OATP1B1 and baricitinib on OATP1B3). The inhibition potential of 21 metabolites (including the active moieties of three prodrugs) was also tested *in vitro* and 11 showed positive results. Using the basic model, prediction *R* values were calculated. Only 3 (23%) drugs had *R* values ≥ 1.1, suggesting a potential to inhibit OATP1B1/3 *in vivo* (**Table 1**), and further clinical evaluations were conducted for two of them. As mentioned in the above section, elagolix co-administration with rosuvastatin, a substrate of BCRP and OATP1B1/3, resulted in a 67% increase in rosuvastatin peak plasma concentration (C_{max}) after single dose, with no change in AUC_{24h} (–12%), whereas multiple doses of elagolix decreased rosuvastatin AUC_{24h} by 41% with comparable C_{max} values. *In vitro* studies suggest that elagolix has the potential to inhibit both OATP1B1/3 and BCRP but the underlying mechanism for the decrease in rosuvastatin exposure after multiple dosing of elagolix is not clear. Based on this observation, it is recommended to consider increasing the dose of rosuvastatin when co-administered with elagolix.[7] For ivosidenib, PBPK simulations were used and predicted no significant effect on rosuvastatin exposure. The inhibition potential of the oncology drug encorafenib on OATP1B1/3 was not investigated clinically.

Renal transporters OAT1/3, OCT2, and MATE1/2-K

Most of the drugs were tested *in vitro* for their potential to inhibit OAT1/3 (*N* = 33) and OCT2 (*N* = 36). Similar assays were conducted for metabolites, including 10 metabolites

for OAT1/3 and 18 for OCT2. Regarding MATE, a relatively smaller number of drugs (N = 23) and metabolites (N = 9) were tested. Fourteen drugs were found to be inhibitors of MATE1, 10 of MATE2-K, 10 of OAT3, 5 of OAT1, 10 of OCT2, and several metabolites also inhibited these transporters (**Figure 1**). The $I_{max,u}/IC_{50}$ ratios were calculated and drugs with ratios greater than the cutoffs (0.1 for OAT1/3 and OCT2, and 0.02 for MATE1/2-K) are presented in **Table 1**. For OAT1/3, four drugs had $I_{max,u}/IC_{50}$ values ≥ 0.1, and only ivosidenib was further studied using PBPK modeling. Ivosidenib was predicted to slightly increase the AUC of co-administered methotrexate (a clinical substrate of OAT1/3) by 36%, with no change in C_{max}. This effect was not considered to be clinically meaningful.[14] Similarly for OCT2, among the three drugs with $I_{max,u}/IC_{50}$ values ≥ 0.1, only bictegravir was further tested *in vivo*. Bictegravir also has the potential to inhibit MATE1 ($I_{max,u}/IC_{50}$ = 0.02). Co-administration with bictegravir significantly increased the AUC and C_{max} of metformin (a clinical substrate of both OCT2 and MATE) by 39% and 28%, respectively. Based on both *in vitro* and clinical results, specific dosing recommendations are provided for concomitant use of substrates of these transporters (e.g., metformin and dofetilide).[15] As for MATE1/2-K, 7 drugs had prediction ratios ≥ 0.02 and 4 (57%) were further tested. Along with bictegravir mentioned above, apalutamide showed weak inhibition of MATE and was predicted to increase the AUC of concomitant metformin by 28%.[16] Overall, no further investigations were conducted for more than half of the drugs with ratios over the cutoffs, and no labeling recommendation was provided except for tafenoquine, for which it is recommended to avoid co-administration of tafenoquine with OCT2 and MATE substrates.[17]

DISCUSSION

The systematic review of transporter inhibition data for drugs approved by the FDA in 2018 found that a total of 13 drug transporters were studied *in vitro* and that *in vitro*-to-*in vivo* predictions using basic models were available for the nine transporters currently recommended for evaluation by the FDA. Among drugs with prediction values greater than the cutoffs and further evaluated *in vivo* (N = 16 drug interactions), 9 (56%) showed positive clinical interactions. Although all the observed or simulated inhibition results were weak (AUCR < 2), seven of the nine interactions (involving five drugs, namely bictegravir, elagolix, fostamatinib, sarecycline, and tezacaftor/ivacaftor) resulted in labeling recommendations. Interestingly, more than half of the drugs with predictions greater than the cutoffs had no further evaluations. This highlights that current basic models represent a useful, simple first step to evaluate the clinical relevance of *in vitro* findings, but that multiple other factors are considered by sponsors and regulators when deciding the need for further clinical evaluations. For example, for efflux transporters, solubility needs to be weighed when calculating I_{gut}/IC_{50} ratios. Among the 11 drugs with I_{gut}/IC_{50} ≥ 10 but not clinically tested, at least 6 drugs (dacomitinib, doravirine, encorafenib, gilteritinib, ivosidenib, and lorlatinib) had low solubility, indicating possible overprediction when using the theoretical intestinal concentration. In addition, for prodrugs, such as baloxavir marboxil, high intestinal concentrations may not be reached due to the fast conversion to their active metabolites. Indeed, when tested in clinical studies with the marker substrates digoxin and rosuvastatin, baloxavir marboxil showed no clinical inhibition of P-gp or BCRP. Importantly, 80% of the drugs in the present data set are orphan drugs and 50% are indicated for cancer treatment. Given the challenges of conducting clinical trials in patients with rare diseases or with advanced stages of cancer, the high number of drugs without clinical evaluations is not surprising.

Four drugs, namely apalutamide and baricitinib (inhibition of OAT3), doravirine (OATP1B/3, OCT2, and MATE1/2-K), and fosnetupitant (OATP1B1/3) had prediction values less than the cutoffs but had clinical evaluations or PBPK simulations available. Consistent with the predictions, all drugs were confirmed not to inhibit these transporters *in vivo* (AUCRs of 0.94–1.09).[12,16,18,19] Although the current sample size is limited, these true negative prediction data support the suitability of the current prediction cutoffs.

Overall, based on all *in vitro*, in *silico*, and clinical evaluations available, drugs approved in 2018 were found to have a relatively limited impact as transporter inhibitors, with all victim AUCRs < 2. However, a significant DDI risk cannot be ruled out for drugs with high prediction values that were not tested clinically.

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1. Lee, S.-C. *et al.* Evaluation of transporters in drug development: current status and contemporary issues. *Adv. Drug Deliv. Rev.* **116**, 100–118 (2017).
2. FDA'sdraftguidanceforindustry:InVitrometabolism-andtransporter-mediateddrug-drug interaction studies (in vitro DDI guidance) (October 2017) <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-metabolism-and-transporter-mediated-drug-drug-interaction-studies-guidance-industry>. Accessed September 18, 2019.
3. US Food and Drug Administration's (FDA's) draft guidance for industry: clinical drug interaction studies—study design, data analysis, and clinical implications (clinical DDI guidance) (October 2017) <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-study-design-data-analysis-and-clinical-implications-guidance>. Accessed September 18, 2019.
4. EMA's Guideline on the Investigation of Drug Interactions (21 June 2012) <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf>. Accessed September 18, 2019.
5. MHLW's guideline on drug interaction for drug development and appropriate provision of information (February 8, 2019) <https://www.mhlw.go.jp/web/t_doc?datald=00tc3525&dataType=1>. Accessed September 18, 2019.
6. Yu, J. *et al.* Mechanisms and clinical significance of pharmacokinetic-based drug-drug interactions with drugs approved by the U.S. Food and Drug Administration in 2017. *Drug Metab. Disp.* **47**, 135–144 (2019).
7. Elagolix (ORILLISA) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/2104500rig1s000TOC.cfm>. Accessed September 18, 2019.

8. Fostamatinib (TAVALLISE) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209299Orig1s000TOC.cfm>. Accessed September 18, 2019.
9. Sarecycline (SEYSARA) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209521Orig1s000TOC.cfm>. Accessed September 18, 2019.
10. Tezacaftor and Ivacaftor (SYMDEKO) labeling and clinical pharmacology biopharmaceutics review(s) (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210491Orig1s000TOC.cfm>. Accessed September 18, 2019.
11. Litman, T. *et al*. The multidrug-resistant phenotype associated with overexpression of the new ABC half-transporter, MXR (ABCG2). *J. Cell Sci.* **113**, 2011–2021 (2000).
12. Doravirine (PIFELTRO) labeling and clinical pharmacology biopharmaceutics review(s) (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210806Orig1s000,210807Orig1s000TOC.cfm>. Accessed September 18, 2019.
13. Stiripentol (DIACOMIT) Labeling and clinical pharmacology biopharmaceutics review(s) (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/206709Orig1s000,207223Orig1s000TOC.cfm>. Accessed September 18, 2019.
14. Ivosidenib (TIBSOVO) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211192Orig1s000TOC.cfm>. Accessed September 18, 2019.
15. Bictegravir, emtricitabine, and tenofovir alafenamide (BIKTARVY) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210251Orig1s000TOC.cfm>. Accessed September 18, 2019.
16. Apalutamide (ERLEADA) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/Erleada_210951_toc.cfm>. Accessed September 18, 2019.
17. Tafenoquine (KRINTAFEL) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210795Orig1s000TOC.cfm>. Accessed September 18, 2019.
18. Baricitinib (OLUMIANT) labeling and clinical pharmacology biopharmaceutics review(s) (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000TOC.cfm>. Accessed September 18, 2019.
19. Fosnetupiant and palonosetron (AKYNZEO) labeling and multi-discipline review/summary, clinical, non-clinical (Drugs@FDA). <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210493Orig1s000ApprovTOC.cfm>. Accessed September 18, 2019.