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Review article

Classification of drugs for evaluating drug interaction in drug development and clinical management

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ABSTRACT

During new drug development, clinical drug interaction studies are carried out in accordance with the mechanism of potential drug interactions evaluated by *in vitro* studies. The obtained information should be provided efficiently to medical experts through package inserts and various information materials after the drug's launch. A recently updated Japanese guideline presents general procedures that are considered scientifically valid at the present moment. In this review, we aim to highlight the viewpoints of the Japanese guideline and enumerate drugs that were involved or are anticipated to be involved in evident pharmacokinetic drug interactions and classify them by their clearance pathway and potential intensity based on systematic reviews of the literature. The classification would be informative for designing clinical studies during the development stage, and the appropriate management of drug interactions in clinical practice.

1. Introduction

In current drug therapy where two or more drugs are routinely coprescribed, physicians and pharmacists need to pay utmost attention to avoid drug interactions (DIs) that may lead to unpleasant adverse events and insufficient drug effects [1]. In this review, DIs include interactions between drug and drug as well as between drug and food/beverage. In the past, some effective drugs unfortunately caused serious adverse events due to unexpected DIs and were withdrawn from the market [2] such as the concomitant use of sorivudine and fluorouracil-based anticancer drugs [3]. In recent decades, the mechanism of pharmacokinetic DIs has been elucidated very well due to advances in pharmacokinetic research, which allows the prediction of the degree of DI for many combinations of drugs [4,5]. By referring to the latest information, the risk of DI is becoming routinely minimized during the screening process; nevertheless, if the potential of a DI is detected during the drug-development process, the information should be appropriately conveyed to physicians and pharmacists.

In Japan, the *Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information* (Japanese guideline) was notified in 2018 by the Ministry of Health, Labour and Welfare [6]. The guideline was implemented through the public consultations as a formal procedure in Japan and by soliciting comments from the regulatory authorities of the United States and Europe. It reflects the latest scientific knowledge and presents the appropriate

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methods for the evaluation of DIs during the development of new drugs and how the risks and information of DIs should be provided to medical experts. The Japanese guideline includes lists of substrates, inhibitors, and inducers of cytochrome P450s (P450s) and transporters, which would be used as index drugs or typical drugs at various steps of DI evaluation in the drug-development process. In this review, we aim to enumerate drugs that were involved or are anticipated to be involved in evident pharmacokinetic DIs and classify them by their clearance pathway and potential intensity from more general viewpoints based on systematic reviews of the literature and similar classifications [7,8]. The lists are restricted to clinically prevalent drugs in Japan, in most cases, which are informative for designing clinical studies during drug development and the appropriate management of DIs in clinical practice.

According to Japanese regulations on package inserts of drugs [9], clinical alerts regarding DIs are classified into "contraindication for co-administration (do not co-administer)" or "precaution for co-administration (be careful about concomitant use)". All drug names that are contraindicated have to be described by their nonproprietary names and representative brand names in the package insert. Alerts regarding DIs classified as "precaution for co-administration" are requested that nonproprietary names or names of drug class are listed in the package insert. For alerts regarding DIs classified as "precaution for co-administration" and metabolized mainly by CYP3A, the guideline requests that the strength classification of CYP3A inhibition or induction is also clarified in the package inserts so that a more systematic and updated management of DIs can be performed depending on the therapeutic effect or pharmacokinetic properties of concomitant drugs. The classifications presented in this review would also be valuable because they provide suggestive information to determine how the drugs should be used in combination in clinical practice and includes the latest available information for medical experts who need systematic knowledge on index drugs and typical drugs of DIs including the strength classification of inhibitors and inducers for P450.

2. Pharmacokinetic theory and limitations to be considered

The significance of DIs was understood even at the dawn of drug metabolism research when P450 was discovered and found to be inducible [10,11]. Then, DIs associated with changes in blood drug concentrations were reported for many cases, but reasonable predictions of DIs were achieved only after isoenzymes of human P450 were identified in the 1980s [12], together with the development of the clearance theory and physiologically based pharmacokinetic (PBPK) analysis [13]. The whole-body clearance, which means the performance of drug elimination from the body is evaluated *in vivo* by dividing the dose by the drug blood concentration area under the curve (AUC) after systemic administration. The whole-body clearance is also equal to the sum of organ clearances, and to calculate organ clearance from intrinsic clearance, which is measurable by *in vitro* experiments, a local organ model, such as the well-stirred model, is necessary to consider the influence of the blood flow passing through. When a drug is administered orally, the oral clearance becomes proportional to the hepatic intrinsic clearance without being affected by the blood flow due to a contribution of the first-pass effect. Thus, the theory suggests that AUC changes of orally administered drugs caused by pharmacokinetic DIs are inversely proportional to changes in the hepatic intrinsic clearance in principle. PBPK analysis would be useful when this simple assumption needs to be adjusted due to more complicated situations.

An inhibitor with a similar strength of inhibitory effect to a specific enzyme of P450 is theoretically expected to change the AUC of a substrate with high specificity for the enzyme to a similar extent, regardless of whether the inhibition is reversible (including competitive) or irreversible (time-dependent). Thus, the classification of inhibitors by the degree of change in the AUC of a particular sensitive substrate is useful to estimate pharmacokinetic DIs with various similar substrates. The substrate used to classify inhibitors should be selective for the pathway of the metabolism to be evaluated. The Japanese guideline defined a substrate showing a 5-fold or greater AUC change in combination with a strong inhibitor as a "sensitive substrate," which means that at least 80% of the oral clearance depends on the route. Similarly, a substrate that exhibits an AUC change from double to 5-fold is defined as a "moderately sensitive substrate," which corresponds to 50−80% dependence. Inhibitors of representative P450s were classified as strong, moderate, or weak depending on the degree of AUC changes of the sensitive substrate in the Japanese guideline on DIs, and these classifications correspond to AUC changes of $\geq$ 5-fold, $\geq$ 2 to < 5-fold, and < 2-fold respectively. In this review, however, weak inhibitors are not described from the viewpoint of clinical interaction management because both the degree of AUC change and the selectivity are sometimes unclear. The classifications and certain terms related to substrate, inhibitor and inducer are described in the Glossary at the end of this manuscript.

The above theory could also be applied to some of the hepatic clearance regulated by transporters, but there are a few points to consider. In the case of a drug that is taken up into the liver via an uptake transporter such as organic anion transporting polypeptide (OATP) 1B, and does not return to the bloodstream at all, the theory can be applied correctly. However, this may be an exceptional case. For most of the substrates of hepatic uptake transporters, hepatic clearance is estimated as a complex function of passive and active uptake, vascular efflux, biliary efflux, and metabolism. Furthermore, transporters are also often expressed in the extrahepatic tissues. As will be described in the "Drugs involved in pharmacokinetic DIs mediated by transporters" section 4, overlapping substrate recognition is an additional issue for the prediction of transporter-mediated pharmacokinetic DIs. Overall, for drugs involved in transporter-mediated DIs, the change in AUC often does not correspond to the intrinsic transporter activity of a particular transporter at a particular location. For this reason, drugs involved in DIs mediated by transporters are classified not by the degree of DI but by transporters in this review.

The mechanism of DIs found in clinical settings can be even more complicated than those assumed in the above theory. In the small intestine, metabolism by CYP3A and efflux transport by P-glycoprotein (P-gp) are often simultaneously involved in DIs. In the Japanese guideline, a formula for estimating the risk of DIs in the small intestine from *in vitro* experiments is described, but this was derived empirically from the relationship between the intensity of the *in vitro* and *in vivo* DIs and does not provide a pharmacokinetic estimate of the drug concentration in the intestinal epithelial cells where the interaction is occurring. Even for advanced models currently used in PBPK analysis, the predictability of DIs in the small intestine has hardly been verified yet because we do not know the precise drug concentrations in the enterocytes and the activity of efflux transporters including P-gp and breast cancer resistance protein (BCRP). At present, for drugs that have a remarkably high metabolic clearance by CYP3A and/or for those transported by P-gp or BCRP extensively, caution should be taken to avoid a higher risk of DI due to the contribution by the small intestine.

The theory of DIs caused by a change in hepatic clearance cannot be applied to drugs that are to be cleared extensively from the extrahepatic tissue. For a representative example, renal clearance is composed of three processes, namely, glomerular filtration, tubular secretion, and reabsorption, and in the case of interaction involving

transporter activity in the processes of secretion and reabsorption, the basic equation differs depending on whether the transporter is located at the basolateral or apical side. In these cases, the most probable prediction would be obtained from a careful analysis using the PBPK model. The degree of DIs is smaller after intravenous, intramuscular, or transdermal administrations of the substrate than that after oral administration, in general due to a lack of the first-pass effect. An analysis by a PBPK model would again be considered effective in these cases.

In this review, drugs were classified based on the largest change in the index parameter observed in their DI studies, as described in the next section. Furthermore, all the classification is based on the average parameter changes observed in clinical studies in primarily healthy subjects. The potential for interstudy and interindividual differences needs to be considered to apply the classification of drugs from this review to a clinical setting. In the pediatric population, especially in those below the age of two years, the development of drug-metabolizing enzymes and transporters is insufficient [14]. In the elderly population, renal and hepatic functions are considerably reduced [15]. Furthermore, pharmacokinetics and DIs are affected by various disease states [16,17]. Because of these variations, DIs can be enhanced potentially by several times. Overall, these uncertainties and exceptions need to be considered carefully when the classification presented in this review is to be applied to clinical practice.

3. Drugs involved in evident pharmacokinetic DIs mediated by P450s

Substrates, inhibitors, and inducers of P450 involved in evident pharmacokinetic DIs were classified according to AUCR (the ratio of AUC in the presence of an interacting drug to that in the absence) after oral doses or the ratio of oral clearance (CL/F) in most cases, which is observed in a clinical DI study with one of the designated *in vivo* index drugs of P450 according to the Japanese guideline. In a few cases, trough and steady-state concentrations were used as described in the table. The guidance issued in 2020 by the United States FDA are also referred to as a regulatory document that defines the same strength classification of P450 inhibition or induction (strong, moderate, or weak inhibitor or inducer).

For examining the drug list, the new drug approval information of Japan (March 31, 2020. http://www.pmda.go.jp/PmdaSearch/iyakuSearch/) and the United States (https://www.accessdata.fda.gov/scripts/cder/daf/), Drug Interaction Solutions' PK-based Drug Interaction Database (DIDB) (http://www.druginteractioninfo.org), and the UCSF-FDA Transportal (http://bts.ucsf.edu/fdatransportal/) were used. Drugs to be considered for each decision tree of the drug-metabolizing enzyme P450 in the Japanese guideline were extracted and classified based on changes in pharmacokinetics in clinical DI studies.

We extracted drugs that could cause interactions accompanied by remarkable (strong) to moderate changes in pharmacokinetics, which are particularly important from the viewpoint of clinical interaction management, and classified drugs with the application of Japanese clinical settings as represented in Tables 1–3. Therefore, the tables exclude drugs that are currently not marketed in Japan, but include clinical index drugs shown in the Japanese guideline.

In Table 3, inducer drugs are listed by each isozyme of P450 because inductions were examined by clinical studies in which an isozyme-selective substrate drug was co-administered. However, inducers are described together at the end of this chapter since several P450 isozymes are frequently induced together.

3.1. Substrates and inhibitors of P450

3.1.1. Substrates and inhibitors of CYP1A2

It has been demonstrated that the AUC of sensitive CYP1A2 substrates notably increased when administered with fluvoxamine (caffeine 13.7-fold, tizanidine 32.7-fold, and ramelteon 128-fold). These evident DIs need to be avoided carefully in clinical settings. It is well-known that fluvoxamine inhibits CYP1A2 as well as CYP2C19. Furthermore, it also inhibits CYP2C9, CYP2D6, and CYP3A4 *in vitro* [18]. Although the degrees of inhibition of fluvoxamine against some of these enzymes *in vivo* are obscure, the observed strong DIs might be related to its broad inhibition specificity for various P450s. For this reason, although fluvoxamine is selected as the index inhibitor of CYP1A2 in the Japanese guideline, the results of a clinical DI study need to be interpreted carefully for the possible contribution of the other P450 enzymes.

3.1.2. Substrates and inhibitors of CYP2B6 and CYP2C8

In the cases of CYP2B6 and CYP2C8, the number of substrates and inhibitors listed in Tables 1 and 2 are relatively small. However, it should be noted that the frequency of pharmacokinetic DIs would be potentially more than those implied by the list because *in vitro* studies have not been carried out routinely for these enzymes until recently, and thus, only limited clinical DI studies have been performed. Although a very strong inhibition of CYP2B6 was observed *in vitro* for some azoles [19,20], no clinical study has been performed to confirm their *in vivo* significance.

Cyclophosphamide is an alkylating agent of cancer activated by CYP2B6 and CYP2C19 [21]. Therefore, the outcome of cyclophosphamide treatment might be affected by DIs as well as the genetic polymorphism with regard to both enzymes [22], although it is not included in Table 1. Bupropion designated as a sensitive clinical substrate of CYP2B6 is not marketed in Japan, thus not included in Table 1. To evaluate CYP2B6-dependent clearance, stereoselective metabolism of bupropion may need to be evaluated [23].

It should be recognized that cerivastatin, an effective HMG-CoA inhibitor, was withdrawn from the market because of severe DI by gemfibrozil. Cerivastatin is a substrate of CYP2C8, and in this evident and fatal DI, it has been reported that glucuronide of gemfibrozil played a critical role in the irreversible inhibition of CYP2C8 [24,25].

3.1.3. Substrates and inhibitors of CYP2C9

Warfarin is the *in vivo* index substrate of CYP2C9, but it should be noted that warfarin is composed of two optical isomers, the S-isomer and R-isomer; the S-isomer is more effective and shows higher selectivity for CYP2C9 than the R-isomer [26]. Therefore, when warfarin is to be used in clinical DI studies, changes in both drug concentrations and efficacy should be observed. In Table 1, S-warfarin is described, considering the evaluation of DI potentials in clinical studies. Recently, miconazole, known as an inhibitor of CYP3A, was contraindicated for use with warfarin in Japan [27] because it also strongly inhibited CYP2C9 and caused severe DI in association with warfarin. Some azole antifungals, including miconazole, often inhibit multiple P450 isoenzymes *in vitro*, but it should be kept in mind that their *in vivo* inhibition potential has not been verified satisfactorily. In the future, further accumulation of information is necessary. Celecoxib is designated as a sensitive clinical substrate of CYP2C9 in the United States, considering the results of pharmacogenetic studies [28].

Although not listed in Table 2, it has been suggested that blood concentrations of losartan, warfarin, and phenytoin were increased

Table 1
Prevalent substrate drugs of P450 which are involved in evident pharmacokinetic drug interactions.

isoform	classification[a]	substrate			concomitantly used inhibitor		comment	ref.
		name[b],[c]	dose[d]	AUCR[e]	name[c]	dose[d]		
CYP1A2	sensitive	**caffeine***	250 mg sd	13.7	fluvoxamine	100 mg qid		S1
		tizanidine*	4 mg sd	9.74	ciprofloxacin	500 mg bid		S2
			4 mg sd	32.7	fluvoxamine	100 mg qd		S3
		duloxetine	60 mg sd	5.60	fluvoxamine	100 mg qd		S4
		melatonin	5 mg sd	17.4	fluvoxamine	50 mg qd		S5
		ramelteon	16 mg sd	128	fluvoxamine	100 mg bid		S6
	moderately sensitive	**clozapine**	50 mg sd	2.84	fluvoxamine	50 mg bid		S7
		pirfenidone	267 mg tid	4.01	fluvoxamine	50 mg qd,bid 50/100 mg bid	non-smoker	S8
		ramosetron	10μg sd	2.66	fluvoxamine	50 mg bid		S9
		theophylline	250 mg sd	2.38	fluvoxamine	75 mg qd		S10
CYP2B6	moderately sensitive	**efavirenz**	100 mg sd	2.24	voriconazole	200 mg bid	upper limit of 90% CI, mean 1.89	S11
CYP2C8	sensitive	**repaglinide***	0.25 mg sd	5.08	clopidogrel	300 mg sd		S12
			0.25 mg sd	8.26	(gemfibrozil)	900 mg sd		S13
		selexipag	400μg sd	11.09	(gemfibrozil)	600 mg bid	active metabolite	S14
	moderately sensitive	**montelukast**	10 mg sd	4.54	(gemfibrozil)	600 mg bid		S15
		pioglitazone	15 mg sd	4.66	(gemfibrozil)	600 mg bid	CYP2C8(*1/*3, *3/*3)	S16
			15 mg sd	3.12	(gemfibrozil)	600 mg bid	CYP2C8(*1/*1)	
CYP2C9	moderately sensitive	**S-warfarin***[f]	0.75 mg/kg sd (warfarin)	4.72	miconazole	125 mg qd	CF/F ratio: 0.19	S17
			0.75 mg sd (warfarin)	2.85	fluconazole	400 mg qd		S18
		celecoxib	200 mg sd	2.31	fluconazole	200 mg qd		S19
		glimepiride	0.5 mg sd	2.38	fluconazole	200 mg qd		S20
		phenytoin	250 mg sd	2.32	fluconazole	400 mg qd	trough (C48)	S21
		(tolbutamide*)	500 mg sd	2.09	fluconazole	100 mg qd		S22
CYP2C19	sensitive	**S-lansoprazole***	60 mg sd (lansoprazole)	14.0	fluvoxamine	25 mg bid	Homo EM Japanese	S23
				6.21			Hetero EM Japanese	
				2.01			PM Japanese	
		omeprazole*	40 mg sd	5.62	fluvoxamine	25 mg bid	Homo EM Japanese	S24
				2.38			Hetero EM Japanese	
				1.15			PM Japanese	
	moderately sensitive	**lansoprazole***	40 mg sd	3.83	fluvoxamine	25 mg bid	Homo EM Japanese	S25
				2.50			Hetero EM Japanese	
				1.04			PM Japanese	
		diazepam	10 mg sd	2.80	fluvoxamine	50/100 mg bid		S26
		etizolam[g]	0.25 mg sd	2.64	PGx		PM/EM Japanese	S27
		rabeprazole	20 mg sd	2.82	fluvoxamine	25 mg bid	Homo EM Japanese	S28
				1.68			Hetero EM Japanese	
				1.07			PM Japanese	
		voriconazole	200 mg bid	2.64	fluconazole	200 mg qd	EM	S29
CYP2D6	sensitive	**(desipramine*)**	50 mg sd	7.43	(fluoxetine)	60 mg qd		S30
			50 mg qd	5.46	paroxetine	30 mg qd		S31
		dextromethorphan*	30 mg bid	47.8	quinidine	75 mg bid		S32
			30 mg sd	27.2	(fluoxetine)	60 mg qd	cocktail study	S33
		(nebivolol*)	10 mg sd	6.57	(fluoxetine)	20 mg qd		S34
			5 mg sd	6.15	paroxetine	20 mg qd		S35
		atomoxetine	20 mg bid	7.06	paroxetine	20 mg qd		S36
		eliglustat	100 mg bid	28.4	paroxetine	30 mg qd	one ultra rapid metabolizer	S37
				10.0			EM	
				5.20			IM	
		metoprolol	100 mg sd (metoprolol)	7.92	paroxetine	20 mg qd	R-metoprolol	S38
				5.08	paroxetine	20 mg qd	S-metoprolol	
		nortriptyline	25 mg bid	5.12	paroxetine	20 mg bid	CL/F	S39
		perphenazine	0.11 mg/kg sd	6.96	paroxetine	20 mg qd		S40
		tolterodine	tolerodine L-tartrate 2 mg bid	11.3	(fluoxetine)	20 mg qd	EM, CL/F	S41
	moderately sensitive	**imipramine**	50 mg sd	3.33	(fluoxetine)	60 mg qd		S42
		propafenone	current daily dose (mean 825 mg)	2.69	quinidine	50 mg tid	Css	S43
		propranolol	20 mg sd	2.29	quinidine	200 mg sd		S44
		tramadol	50 mg sd	2.15	terbinafine	250 mg qd		S45
		trimipramine	75 mg sd	2.98	quinidine	100 mg sd	CL/F (n = 2)	S46
		venlafaxine	75 mg sd	3.27	terbinafine	250 mg qd		S47
CYP3A	sensitive	**midazolam***	4 mg sd	7.00	clarithromycin	500 mg bid		S48
			7.5 mg sd	10.8	itraconazole	200 mg qd		S49
			7.5 mg sd	15.9	(ketoconazole)	400 mg qd		
		triazolam*	0.25 mg sd	27.1	itraconazole	200 mg qd		S50

Table 1 (*continued*)

isoform	classification[a]	substrate			concomitantly used inhibitor		comment	ref.
		name[b],[c]	dose[d]	AUCR[e]	name[c]	dose[d]		
			0.25 mg sd	22.4	(ketoconazole)	400 mg qd		
			0.125 mg sd	5.25	clarithromycin	500 mg bid		S51
		blonanserin	2.5 mg sd	17.4	(ketoconazole)	400 mg qd		S52
		brotizolam	0.5 mg sd	5.10	itraconazole	200 mg qd		S53
		budesonide	3 mg sd	6.81	(ketoconazole)	200 mg qd		S54
		darunavir[h]	400 mg sd	10.7	ritonavir	100 mg bid		S55
		dasatinib	20 mg qd	6.13	(ketoconazole)	200 mg bid	Upper limit of 90% CI, mean 4.84	S56
		ebastine	20 mg qd	42.5	(ketoconazole)	400 mg qd		S57
		eletriptan	80 mg sd	5.87	(ketoconazole)	400 mg qd		S58
		entrectinib	100 mg sd	6.04	itoraconazole	100 mg qd		S59
		eplerenone	100 mg sd	5.39	(ketoconazole)	200 mg bid		S60
		everolimus	2 mg sd	14.7	(ketoconazole)	200 mg bid		S61
		felodipine	5 mg sd	6.34	itoraconazole	200 mg qd		S62
		ivabradine	10 mg sd	7.70	(ketoconazole)	200 mg qd		S63
		ibrutinib	40 mg sd	26.2	(ketoconazole)	400 mg qd		S64
		lomitapide	60 mg sd	27.3	(ketoconazole)	200 mg bid		S65
		lurasidone	10 mg sd	8.95	(ketoconazole)	400 mg qd		S66
		maraviroc	100 mg bid	5.00	(ketoconazole)	400 mg qd		S67
		nisoldipine	5 mg sd	25.3	(ketoconazole)	200 mg qd		S68
		quetiapine	25 mg sd	6.20	(ketoconazole)	200 mg qd		S69
		rupatadine	20 mg qd	11.6	(ketoconazole)	200 mg qd		S70
		sildenafil	100 mg sd	9.36	(saquinavir)/ ritonavir	1200 mg tid/500 mg bid		S71
		simvastatin	40 mg sd	12.6	(ketoconazole)	400 mg qd		S72
		sirolimus	0.5−2 mg eod	26.1	(telaprevir)	1125 mg bid		S73
		ticagrelor	90 mg sd	7.32	(ketoconazole)	200 mg bid		S74
		tolvaptan	30 mg sd	5.40	(ketoconazole)	200 mg qd		S75
		vardenafil	5 mg sd	9.94	(ketoconazole)	200 mg qd		S76
	moderately sensitive	**alprazolam**	1 mg sd	3.98	(ketoconazole)	200 mg bid		S77
		aprepitant	125 mg sd	4.78	(ketoconazole)	400 mg qd		S78
		atorvastatin	80 mg qd	4.45	clarithromycin	500 mg bid		S79
			20 mg sd	2.50	itraconazole	200 mg qd		S80
		ceritinib	450 mg sd	2.88	(ketoconazole)	200 mg bid		S81
		colchicine	0.6 mg sd	2.87	(ketoconazole)	200 mg bid		S82
		cyclosporin A	0.59 mg/kg bid	4.39	(ketoconazole)	200 mg qd		S83
		doravirine[h]	100 mg sd	3.06	(ketoconazole)	400 mg qd		S84
		eliglustat	100 mg bid	4.40	(ketoconazole)	400 mg qd		S37
		lapatinib	100 mg sd	3.67	(ketoconazole)	200 mg bid		S85
		lemborexant	10 mg sd	3.70	itraconazole	200 mg qd		S86
		methyl predonisolone	48 mg sd	2.53	itraconazole	200 mg qd		S87
		naldemedine	0.2 mg sd	2.91	itraconazole	200 mg qd		S88
		pimozide	6 mg sd	2.12	clarithromycin	500 mg bid		S89
		rivaroxaban	10 mg qd	2.58	(ketoconazole)	400 mg qd		S90
		tacrolimus	3 mg sd	3.32	itraconazole	200 mg bid		S91
		tadalafil	20 mg sd	4.12	(ketoconazole)	400 mg qd		S92

Note. The table is prepared to provide examples and drugs listed in the table is restricted to clinically prevalent drugs in Japan. The table is not intended to be an exhaustive list. Other elimination pathways may also contribute to the elimination of the substrates listed and should be considered when assessing the drug interaction potential. Some drugs not on the list may also be considered when assessing the drug interaction potential. (e.g. cyclophosphamide is mainly activated by CYP2B6, therefore inhibition of CYP2B6 may result in *in vivo* drug interaction. Clopidogrel is mainly activated by CYP2C19, therefore, inhibition of CYP2C19 in addition to its polymorphism affects the effect). A list of references for the tables are provided in the appendix.

[a] Classification is in principle based on the largest observed AUC change (worst case scenario) in the study with a clinical index inhibitor. Sensitive: AUC increase by ≥ 5-fold (CL/F decrease to <1/5) when co-administered with a strong inhibitor. Moderately sensitive: AUC increase by ≥ 2-fold but <5-fold (CL/F decrease to <1/2 but ≥1/5) when co-administered with a strong inhibitor.

[b] Asterisk (*) represents clinical index substrate.

[c] Drugs in parenthesis are not approved in Japanese market currently.

[d] Multiple doses were given for qd, bid, tid, and eod (every other day). Abbreviation sd and md refers to single dose and multiple dose, respectively.

[e] AUCR is the ratio of AUC in the presence of an interacting drug to that in the absent.

[f] Warfarin is composed of S and R isomers. S-isomer is pharmacologically more potent and selective for CYP2C9. Racemic warfarin: moderate sensitive.

[g] Etizolam is a substrate of CYP2C19 and CYP3A, and CYP3A mediated DDI is potentiated considerably in poor metabolizers of CYP2C19.

[h] Usually administered in combination with ritonavir.

due to concomitant use of 5-fluorouracil-related anticancer drugs, which may include TS-1, UFT, tegafur, fluorouracil, doxifluridine, capecitabine, and carmofur [29,30]. They are not mentioned in the list because fluorouracil does not directly inhibit CYP2C9 *in vitro* [31]. It was surmised that fluorouracil decreases the expression of CYP2C9 in the liver by some unknown mechanism [32]. Similar interaction by fluorouracil has also been suggested for CYP2C19 [33]. Therefore, it is recommended to regard fluorouracils as if they are strong inhibitors of CYP2C9 and CYP2C19 for proper clinical management of DIs.

3.1.4. Substrates and inhibitors of CYP2C19

Strong inhibitors of CYP2C19 in the list include fluvoxamine and fluconazole, but it should be noted that fluvoxamine is also an

Table 2
Prevalent inhibitor drugs of P450 which cause evident pharmacokinetic drug interactions.

isoform	classification[a]	inhibitor		concomitantly used substrate			comment	ref.
		name[b,c]	dose[d]	name[c]	dose[d]	AUCR[e]		
CYP1A2	strong	**fluvoxamine***	100 mg bid	caffeine	250 mg sd	13.7		S1
			100 mg qd	tizanidine	4 mg sd	32.7		S3
		ciprofloxacin	500 mg bid	tizanidine	4 mg sd	9.74		S2
	moderate	**mexiletine**	50 mg tid	tizanidine	2 mg sd	3.42		S93
		oral contraceptives	gestodene 75 μg sd + EE 20-30 μg qd	tizanidine	4 mg sd	3.92		S94
CYP2C8	strong	**clopidogrel***	300 mg sd	repaglinide	0.25 mg sd	5.08	index drug	S95
		(gemfibrozil*)	900 mg sd	repaglinide	0.25 mg sd	8.26		S96
	moderate	**clopidogrel**	75 mg qd	repaglinide	0.25 mg sd	3.95	clinical drug	S95
		deferasirox	30 mg/kg qd	repaglinide	0.5 mg sd	2.27		S97
		teriflunomide	14 mg qd	repaglinide	0.25 mg sd	2.28		S98
CYP2C9	moderate	**fluconazole***	400 mgqd	S-warfarin	warfarin 17.5 mg sd	2.54		S99
		amiodarone	200 mg bid	S-warfarin	warfarin 1.5 mg/kg sd	2.11		S100
		bucolome	300 mg qd	S-warfarin	warfarin 1.4 mg/kg qd	3.29	CL/F	S101
		miconazole[f]	125 mg qd	S-warfarin	warfarin 0.75 mg/kg sd	4.72		S102
CYP2C19	strong	**fluvoxamine***	25 mg bid	omeprazole	40 mg sd	5.62	homo EM (Japanese)	S24
			87.5 mg qd	(S-mephenytoin)	100 mg sd	9.89	EM	S103
		fluconazole	100 mg qd	omeprazole	20 mg sd	6.29		S104
		ticlopidine	200 mg qd	omeprazole	20 mg sd	6.22	homo EM (Japanese)	S105
CYP2D6	strong	**(fluoxetine*)**	60 mg qd	(desipramine)	50 mg sd	7.43		S30
			60 mg qd	dextromethorphan	30 mg sd	27.2	cocktail study	S33
			20 mg qd	nebivolol	10 mg sd	6.57		S34
		paroxetine*	30 mg qd	(desipramine)	50 mg qd	5.46		S31
			20 mg bid	nebivolol	5 mg sd	6.15		S35
		dacomitinib	45 mg sd	dextromethorphan	30 mg sd	9.55		S106
		quinidine	75 mg bid	dextromethorphan	30 mg bid	47.8		S32
			200 mg sd	dextromethorphan	10 mg sd	14.3	cocktail study	S107
		terbinafine	250 mg qd	(desipramine)	50 mg sd	5.69	CL/F	S108
	moderate	**mirabegron***	100 mg qd	(desipramine)	50 mg sd	3.13		S109
			160 mg qd	metoprolol	100 mg sd	3.16		
		cinacalcet	90 mg qd	(desipramine)	50 mg sd	3.12		S110
			50 mg qd	dextromethorphan	30 mg sd	4.93		S111
		abiraterone	1000 mg qd	dextromethorphan	30 mg sd	2.87		S112
		duloxetine	60 mg bid	(desipramine)	50 mg sd	2.92		S113
		escitalopram	20 mg qd	(desipramine)	50 mg sd	2.07		S114
CYP3A	strong ≥10	**itraconazole***	200 mg qd	midazolam	7.5 mg sd	10.8		S49
			200 mg qd	triazolam	0.25 mg sd	27.1		S50
		cobicistat	200 mg qd	midazolam	5 mg sd	19.0		S115
		grapefruit juice[g] **(double strength)**	240 mL tid	midazolam	2 mg sd	5.95		S116
			200 mL tid	simvastatin	60 mg sd	16.1		S117
		ritonavir[h]	100 mg (3 doses)	midazolam	3 mg sd	26.4		S118
			200 mg bid	triazolam	0.1875 mg sd	40.7		S119
		voriconazole[i]	200 mg bid	midazolam	3 mg sd	9.63		S120
			200 mg bid	midazolam	7.5 mg sd	10.3		S121
	strong ≥5, <10	**clarithromycin***	500 mg bid	midazolam	4 mg sd	7.00		S48
			500 mg bid	simvastatin	40 mg qd	9.95		S79
			500 mg bid	triazolam	0.125 mg sd	5.26		S51
		ceritinib	750 mg qd	midazolam	2.5 mg sd	5.42		S81
		posaconazole	200 mg qd	midazolam	2 mg sd	5.70		S122
	moderate	**erythromycin***	500 mg bid	triazolam	0.125 mg sd	3.80		S51
		fluconazole*	200 mg qd	triazolam	0.25 mg sd	4.42		S123
		verapamil*	80 mg tid	midazolam	15 mg sd	2.92		S124
			80 mg tid	simvastatin	40 mg sd	4.65		S125
		aprepitant	80 mg qd	midazolam	2 mg sd	3.29		S126
		ciprofloxacin	500 mg sd	sildenafil	50 mg sd	2.12		S127
		crizotinib	250 mg bid	midazolam	2 mg sd	3.65		S128
		cyclosporine A	203 mg/day	midazolam	2 mg sd	2.21	stable therapy	S129
		diltiazem	60 mg tid	midazolam	2 mg sd	4.06		S130
			60 mg tid	triazolam	0.25 mg sd	3.38		S131
		fluvoxamine	100 mg qd	(buspirone)	10 mg sd	2.35		S132
		fosravuconazole	200 mg qd	midazolam	2 mg sd	3.01		S133
		imatinib	400 mg qd	simvastatin	40 mg sd	2.92		S134

Table 2 (*continued*)

isoform	classification[a]	inhibitor		concomitantly used substrate			comment	ref.
		name[b,c]	dose[d]	name[c]	dose[d]	AUCR[e]		
		tofisopam	100 mg tid	midazolam	7.5 mg sd	2.36		S135

Note. The table is prepared to provide examples and drugs listed in the table is restricted to clinically prevalent drugs in Japan. The table is not intended to be an exhaustive list. Some drugs not on the list may also be considered when assessing the drug interaction potential. (e.g. 5-Fluorouracil related drugs such as TS-1, UFT, tegafur, fluorouracil, doxifluridine, capecitabine, and carmofur, do not inhibit CYP2C9 directly but may reduce its activity *in vivo* considerably). A list of references for the tables are provided in the appendix.

[a] Classification is in principle based on the largest observed AUC change (worst case scenario) in the study with a sensitive substrate. Strong: AUC increase of sensitive substrate by ≥ 5-fold (CL/F decrease to <1/5). Moderate: AUC increase of sensitive substrate by ≥ 2-fold but <5-fold (CL/F decrease to <1/2 but ≥1/5).

[b] Asterisk (*) represents clinical index inhibitor.

[c] Drugs in parenthesis are not approved in Japanese market currently.

[d] Multiple doses were given for qd, bid and tid. Abbreviation sd and md refers to single dose and multiple dose, respectively.

[e] AUCR is the ratio of AUC in the presence of an interacting drug to that in the absent. Values in parenthesis are data in special population for reference.

[f] Miconazole inhibits various isoenzymes strongly *in vitro* including CYP3A in addition to CYP2C9.

[g] The effect of grapefruit juice varies widely among brands and depends on concentration, dose and preparation.

[h] Usually given in combination with other anti-HIV or anti-HCV drugs. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

[i] Voriconazole inhibits various isoenzymes strongly *in vitro* including CYP2C9 and CYP2C19 in addition to CYP3A.

Table 3
Prevalent inducer drugs of P450 which cause evident pharmacokinetic drug interactions.

isoform	classification[a]	inducer		concomitantly used substrate			comment	ref.
		name[b,c]	dose[d]	name[c]	dose[d]	AUCR[e]		
CYP1A2	moderate	**phenytoin**	300–600 mg/day	caffeine	140 mg sd	0.42	Caffeine CL	S136
		ritonavir[f]	400 mg bid	caffeine	200 mg sd	0.25	cocktail study	S137
		rifampicin	600 mg qd	tizanidine	4 mg sd	0.46		S138
		smoking	not provided	pirfenidone	801 mg sd	0.50		S8
			1-2 pack/day cigarettes	theophylline	3–5 mg/kg sd	0.44	CL/F	S139
		teriflunomide	14 mg qd	caffeine	100 mg sd	0.45		S98
CYP2B6	strong	**carbamazepine**	942 ± 254 mg	(bupropion)	150 mg sd	0.10		S140
	moderate	**rifampicin***	600 mg qd	efavirenz	600 mg sd	0.46		S141
			600 mg qd	efavirenz	600 mg sd	0.44		S142
		efavirenz	600 mg qd	(bupropion)	150 mg sd	0.45		S143
CYP2C8	moderate	**rifampicin***	600 mg qd	repaglinide	4 mg sd	0.20		S144
			600 mg qd	pioglitazole	30 mg sd	0.46		S145
CYP2C9	moderate	**rifampicin***	600 mg qd	celecoxib	200 mg sd	0.35		S146
			300 mg bid	warfarin	0.75 mg sd	0.26		S147
		enzalutamide	160 mg qd	warfarin	10 mg sd	0.44	cocktail study	S148
CYP2C19	strong	**rifampicin***	600 mg qd	omeprazole	5 mg sd	0.11	cocktail study	S149
			600 mg qd	voriconazole	200mgbid	0.01		S150
		apalutamide	240 mg qd	omeprazole	40 mg sd	0.15		S151
	moderate	**enzalutamide**	160 mg qd	omeprazole	20 mg sd	0.30	cocktail study	S148
		phenytoin	300 mg qd	voriconazole	200 mg bid	0.28		S152
CYP3A	strong	**phenytoin***	200–450 mg qd	nisoldipine	40 mg sd	0.11	chronic phenytoin monotherapy	S153
			100 mg tid	quetiapine	250 mg tid	0.20		S154
		rifampicin*	600 mg qd	midazolam	15 mg sd	0.02		S155
			600 mg qd	triazolam	0.5 mg sd	0.05		S156
		apalutamide	240 mg qd	midazolam	2 mg sd	0.08		S151
		carbamazepine	200 mg bid	quetiapine	300 mg bid	0.13		S69
		enzalutamide	160 mg qd	midazolam	2 mg sd	0.14	cocktail study	S148
		mitotane	0.5, 1.0 or 3.5g tid	midazolam	7.5 mg sd	0.05	chronic mitotane therapy	S157
		St. John's wort	200 mg bid	midazolam	3 mg sd	0.18		S158
	moderate	**bosentan**	125 mg bid	sildenafil	100 mg sd	0.31		S159
		efavirenz	600 mg qd	(alfentanil)	43 μg/kg sd	0.24		S160
		etravirine	200 mg bid	maraviroc	300 mg bid	0.47		S161
		modafinil	400 mg qd	triazolam	0.125 mg sd	0.42		S162
		phenobarbital primidone[g]	100 mg qd	nifedipine	20 mg sd	0.39	phenobarbital sodium 100 mg cocktail study	S163
		rifabutin	300 mg qd	midazolam	2 mg sd	0.31	cocktail study	S164

Note. The table is prepared to provide examples and drugs listed in the table is restricted to clinically prevalent drugs in Japan. The table is not intended to be an exhaustive list. A list of references for the tables are provided in the appendix.

[a] Classification is in principle based on the largest observed AUC change (worst case scenario) in the study with a sensitive substrate. Strong: AUC decrease of sensitive substrate to ≤1/5 (CL/F increase by > 5-fold). Moderate: AUC decrease of sensitive substrate by ≤ 1/2 but >1/5 (CL/F increase by ≥ 2-fold but < 5 fold).

[b] Asterisk (*) represents clinical index inducer.

[c] Drugs in parenthesis are not approved in Japanese market currently.

[d] Multiple doses were given for qd, bid and tid. Abbreviation sd and md refers to single dose and multiple dose, respectively.

[e] AUCR is the ratio of AUC in the presence of an interacting drug to that in the absent. Values in parenthesis are data in special population for reference.

[f] Moderate inducer of CYP1A2 with dose of 800 mg/day ritonavir (not with other anti-HIV drugs). Effect on CYP1A2 at lower doses of ritonavir is unknown.

[g] Primidone is partially metabolized to phenobarbital.

inhibitor of CYP1A2 and CYP3A, and fluconazole is also an inhibitor of CYP2C9 and CYP3A. The results of clinical trials that use these drugs as inhibitors need to be interpreted carefully considering the clearance pathway of the substrate concomitantly used. Regarding the clearance by CYP2C19, individual variability due to genetic polymorphism needs to be carefully considered in Asians, including the Japanese. Although it is not included in the list as a substrate of CYP2C19, clopidogrel is a prodrug and CYP2C19 is involved in the production of the active form of clopidogrel. Therefore, the therapeutic benefit of clopidogrel is dependent on both polymorphism and the DI relating to CYP2C19 [34]. In the antiplatelet treatment using clopidogrel, concomitant use of omeprazole is often avoided because omeprazole inhibits CYP2C19 to some extent [35], although the inhibition is not evident as listed in Tables 1 and 2 . Genetic polymorphism of CYP2C19 needs to be considered more seriously in Japanese people, because it is known that nearly 20% of Japanese people completely lack the activity of CYP2C19 [36].

DIs in patients with a genetic variant of a drug-metabolizing enzyme may critically differ from those in usual patients with the wild genotype. For example, in patients lacking CYP2C19 activity, it is apparent that no DI appears even when an inhibitor of CYP2C19 is used in combination. In contrast, a far more evident DI might appear when an inhibitor of the other P450s is used in these patients. Etizolam is a drug that is metabolized by CYP2C19 and CYP3A4. When a strong inhibitor of CYP3A4 is given in combination with extensive metabolizers (EMs) of CYP2C19, the AUC of etizolam is raised by barely less than double [37], but when the same inhibitor is given to poor metabolizers (PMs) of CYP2C19, it has been reported that the AUC of etizolam increased to approximately 6-fold compared with the AUC in EMs without the concomitant drug [38]. In the case of a drug having a significant metabolic contribution by polymorphic P450 enzymes, individual differences of DIs may need to be considered.

3.1.5. Substrates and inhibitors of CYP2D6

In contrast to CYP2C19, it is often considered that individual differences in clearance of CYP2D6 is less in Asians than in Westerners, because the frequency of PM of CYP2D6 is very small in Asians. However, it has been demonstrated that the *CYP2D6*10* mutation in Asians is almost as abundant as the wild type, and the CYP2D6 clearance is greatly diminished in this mutation [39,40]. The homozygotes or heterozygotes of *CYP2D6*10* are often classified as intermediate metabolizers (IMs), but this classification is inconsistent among clinical studies. Special consideration would be necessary for Asians for individual differences in clearance and DI to be noticed, not only for drugs metabolized majorly by CYP2C19, but also those metabolized by CYP2D6.

Eliglustat tartrate, a drug for the treatment of type 1 Gaucher disease, is a typical example that needs such consideration [41]. The prevalence of Gaucher disease is extremely low, approximately one in 50,000 to 100,000 people globally. The AUC of eliglustat in PM of CYP2D6 was 11.2-fold of EM according to the product labeling, so the contribution of CYP2D6 to the metabolism of this drug is clear. In EM of CYP2D6, the AUC of eliglustat was increased 10-fold when co-administered with paroxetine, as shown in Table 1. Because the approved dosage and DI management of eliglustat vary by the genotype of CYP2D6 in Japan as well as in the United States and Europe [42], its use requires genetic testing for CYP2D6. In EM, it is contraindicated for use with a combination of both CYP2D6 and CYP3A inhibitors (moderate or strong), but in IM or PM, it is contraindicated simply with a CYP3A inhibitor (moderate or strong). According to the classification in the clinical trial conducted for this drug, the homozygote of *CYP2D6*10* was classified as IM but the heterozygotes with the wild type were classified as EMs.

3.1.6. Substrates and inhibitors of CYP3A

As is evident from Tables 1–3, there are far more substrates, inhibitors, and inducers that can be involved in DIs mediated by CYP3A than those by the other P450 enzymes. Because DIs occur depending on the prescription frequency of both interacting and affected drugs, many of the pharmacokinetic DIs encountered in clinical settings would be mediated by CYP3A. Therefore, especially for CYP3A, it is essential systematically to avoid DIs based on the classification shown in Tables 1–3 Clinical trials of interactions due to the inhibition of CYP3A were often conducted with ketoconazole. However, because ketoconazole is not currently used as an oral formulation in Japan and the United States FDA does not recommend its use due to safety issues, it is necessary to use other drugs such as itraconazole in clinical trials. There are several azoles other than the two mentioned above that strongly inhibit CYP3A, but care must be taken because P450 isoenzymes other than CYP3A are also often inhibited strongly by some other azoles. Furthermore, it should also be considered that because azoles, including ketoconazole and itraconazole, often inhibit P-gp and BCRP as well as CYP3A, the observed intestinal interactions would not be due to CYP3A inhibition alone.

Major CYP3A isoenzymes in the adult population are CYP3A4 and CYP3A5 [43,44]. In Japan, CYP3A5 is genetically deficient in approximately one-third of the population [45]. Because the substrate recognition or inhibition selectivity between CYP3A4 and CYP3A5 often does not differ significantly, it is generally considered that the individual fluctuations in DI due to polymorphism of CYP3A5 are not significant. However, because it has been reported that some substrates are metabolized preferentially by either CYP3A4 or CYP3A5 [46], and some inhibitors demonstrated selective inhibition of these isoenzymes [47], special consideration might be necessary for these drugs in the future.

CYP3A is expressed in the small intestine as well as in the liver. Thus, the observed CYP3A-mediated DI is the sum of the contribution by the small intestine and the liver. Drugs that are considerably metabolized in the small intestine are often rapidly metabolized by CYP3A *in vitro* [48], and care should be taken to avoid the risk of significant DIs for those drugs. Vice versa, drugs that are susceptible to *in vivo* inhibition of CYP3A with $\geq$10-fold increase in the AUC need to be considered for a notable metabolic contribution by the small intestine [49]. Grapefruit juice is the only beverage listed in Table 2 as a strong inhibitor of CYP3A, and its inhibition is considered to be limited to the small intestine [50]. The DI reports of grapefruit juice vary considerably according to the amount and frequency of the intake, and the results showing strong interaction have been obtained on the condition of ingesting a large amount of dense grapefruit juice, such as double strength [51]. Grapefruit juice should be avoided to reduce DI risk, but medical experts need to know that the risk depends on the amount of intake.

3.2. Inducers of P450

The induction of drug-metabolizing enzymes occurs by the action of nuclear receptors, and pregnane X receptor (PXR), constitutive androstane receptor (CAR), and aryl hydrocarbon receptor (AhR) are particularly important nuclear receptors, among many, in the regulation of pharmacokinetics. These nuclear receptors increase the expression of multiple P450 isoenzymes in varied degrees; PXR increases expressions of CYP2C9, CYP2C19, CYP2B6, and CYP3A, CAR increases those of CYP2B6, CYP2C8, CYP2C9, and CYP3A4, and AhR increases the expression of CYP1A2 [52,53]. In addition, one inducer often shows affinity to multiple nuclear receptors. Because of these properties, the same drug is often listed as an inducer of CYP1A, CYP2B, CYP2C, and CYP3A, as shown in

Table 3. Furthermore, it is known that PXR also increases the expression of transporters such as P-gp and multidrug resistance-associated protein 2 (MRP2), and CAR increases the expression of other metabolic enzymes such as UDP-glucuronosyltransferase (UGT) and sulfotransferase. CYP1A2 is induced via AhR also by smoking but the inducibility is influenced by polymorphisms in CYP1A2, transcription factors and nuclear receptors [54].

In a typical drug-development process, the induction of P450 is often detected by increased mRNA expressions of CYP1A2, CYP2B6, and CYP3A in cell-based assays because of the selectivity of nuclear receptors and detection sensitivity, and this method is also recommended in the new guideline. For inductions via PXR or CAR, an increase of CYP3A mRNA is usually detected in this method. The induction of CYP3A is then evaluated in clinical studies as the next step, and if the result is positive, the drug might be recognized as an inducer but only for CYP3A. In this case, medical experts had better consider the possibility of induction of the related enzymes and transporters as well as CYP3A. This may also be true for a drug listed as an inducer of the P450 isoenzymes other than CYP3A in Table 3.

Currently, inductions of the hepatic enzyme and the intestinal enzyme are not distinguished clearly in the process of drug development, and human hepatocytes are primarily used for *in vitro* studies [55]. However, becauase the expression of nuclear receptors differs considerably between the liver and small intestine, it might be more relevant to consider an intestine-specific induction in the future. It has been reported that vitamin D receptor is an important nuclear receptor that regulates the expression of CYP3A in the intestine [56].

4. Drugs involved in pharmacokinetic DIs mediated by transporters

As with drugs involved in evident pharmacokinetic DIs mediated by P450s, the new drug approval information of Japan (March 31, 2020. http://www.pmda.go.jp/PmdaSearch/iyakuSearch/) and the United States (https://www.accessdata.fda.gov/scripts/cder/daf/), the drug-interaction database, DIDB (http://www.druginteractioninfo.org), and the UCSF-FDA Transportal (http://bts.ucsf.edu/fdatransportal/), were used to enumerate drugs involved in *in vitro* and *in vivo* DI mediated by transporters. Changes in pharmacokinetics were mainly examined with a study conducted by oral administration with AUCR as an indicator. Regarding the transporter, studies with intravenous administration and pharmacokinetic parameters other than AUC were also considered if quantitative information on AUCR was not available in the previous reports. As a general feature of substrates and inhibitors of drug transporters, they are often recognized by multiple transporters because of very broad substrate specificities for each transporter that overlap one another. For example, BCRP can recognize a wide variety of drugs with diverse physicochemical properties, such as molecular weight (MW) (e.g., urate, MW = 168 vs. pheophorbide A, MW = 593) and net charge at neutral pH (7.4) (e.g., anion [rosuvastatin, etc.], cation [imatinib, etc.], and neutral [prazosin, etc.]). The same is true for P-gp and MRP2. Such characteristics are beneficial for the efficient vectorial transport of drugs in the intestine, liver, and kidney because multiple uptake and efflux transporters expressed on the opposite side of epithelial cells can accept the same compound as a substrate. [57]. Moreover, substrate specificities of both OATP1B family transporters in the liver and organic anion transporter 3 (OAT3) in the kidney are very similar (e.g., HMG-CoA reductase inhibitors [statins], angiotensin II receptor antagonist [sartans]).

Therefore, different from P450 substrates/inhibitors/inducers, “clinical index drugs” cannot be clearly defined for transporter substrates/inhibitors because of the significant overlapping of substrate recognition among different transporters. Instead, the current Japanese DI guideline shows examples of “*in vivo* typical substrates/inhibitors” of transporters (Tables 2−3 and 2−4 in the Japanese guideline). They are selected mainly based on clinical evidence such as outcomes of clinical PK-DI studies with “relatively” selective substrates/inhibitors or clinical pharmacogenetic studies for specific genetic polymorphisms of a transporter, which have been known to affect its transport activity as well as acceptable pharmacokinetic and safety profiles of drugs. Thus, when the need for clinical DI studies is considered based on the final judge of decision trees for the evaluation of the possibility of the investigational drug being a substrate/inhibitor of transporters (Figs. 2−1 to 2−7 in the Japanese guideline), the use of “*in vivo* typical substrates/inhibitors” of transporters listed in Tables 2−3 and 2−4 in the Japanese guideline is recommended. Drugs listed in these tables are selected by multiple criteria. The basic concept of the major criteria in the Japanese DI guideline is almost the same as that for the FDA guideline such as *in vitro* experimental evidence and *in vivo* clinical DI outcomes, although the creation of these tables was first initiated independently. However, we also consider multiple factors such as the approval status and clinical usage of drugs in Japan, and the rarity of the drugs with a profile that selectively inhibits the transporters. Therefore, some drugs are differently listed in the Japanese DI guideline and the United States FDA's website. Our current opinions on these drugs are shown in each subsection.

Because scientific knowledge for drug transporters is still being continuously updated, it should be noted that Tables 2−3 and 2−4 never provide exhaustive lists of drugs, and they do not limit the use of other drugs as substrates/inhibitors for a certain transporter if reasonable scientific evidences are provided. Tables 4 and 5 represent the same sets of drugs that appear in the current Japanese DI guideline (Tables 2−3 and 2−4 in the guideline) with detailed study designs and outcomes (AUCR) of the examples of representative clinical PK-DI studies, which can support the validity of studied drugs as *in vivo* sensitive probes/inhibitors for specific transporters, although they are often recognized by other transporters and metabolizing enzymes. So, we should always take care to interpret the major cause of transporter-mediated DIs by integrating the clinical outcomes with other supportive *in vitro* and *in vivo* evidence for a specific combination of interacting and affected drugs.

4.1. Notes for the selection of in vivo typical substrates of transporters (Table 4)

The United States FDA showed similar types of drug lists on their website (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1); a part of the substrate drugs for each transporter is different from those in the Japanese DI guideline (Table 2-3 in the guideline) because of the difference in the inclusion criteria.

4.1.1. Substrates of P-gp

P-gp can accept a wide variety of structurally diverse compounds regardless of their charge and molecular weight and actively pump them out. P-gp is expressed at the apical side of various tissues such as the intestine, liver, and kidney, and physiological barriers such as the blood-brain barrier (BBB) and blood-placental barrier and contributes to the protection of important sections of the body against exposure to xenobiotics. P-gp works not only for the suppression of intestinal absorption of orally administered drugs, but for the enhanced biliary and renal excretion of digoxin and for the decreased brain exposure of drugs such as ivermectin and cyclosporin A.

Table 4
Examples of transporter-mediated pharmacokinetic drug interactions for substrates listed in Japanese guideline.

isoform	substrate			concomitantly used inhibitor		comment[b]	ref.
	name	dose[a]	AUCR[b]	name[c]	dose[a]		
P-gp[d]	**dabigatran etexilate**	150 mg sd	2.43 (dabigatran)	verapamil	120 mg sd	Verapamil was administered 1h before the administration of dabigatran etexilate.	S165
	digoxin	0.4 mg qd	2.65	quinidine	600 mg bid		S166
	fexofenadine	25 mg sd	2.14	quinidine	200 mg sd	cocktail study	S149
		120 mg sd	2.51	verapamil	80 mg tid		S167
	aliskiren	75 mg sd	4.79	cyclosporin A	600 mg sd		S168
		300 mg sd	1.78	verapamil	240 mg qd		S169
	ambrisentan	5 mg qd	2.21	cyclosporin A	100–150 mg bid		S170
	colchicine	0.6 mg sd	3.17	cyclosporin A	100 mg sd		S82
		0.6 mg sd	3.15	cyclosporin A	100 mg sd		S171
		0.6 mg sd	1.88	verapamil	240 mg qd		S82
	everolimus	2 mg sd	3.41	verapamil	80 mg tid		S172
	lapatinib	100 mg sd	3.67	ketoconazole	200 mg bid		S85
	maraviroc	100 mg bid	5.00	ketoconazole	400 mg qd		S67
	nilotinib	200 mg sd	3.11	ketoconazole	400 mg qd		S173
	saxagliptin	20 mg sd	3.67	ketoconazole	200 mg bid		S174
		100 mg sd	2.45	ketoconazole	200 mg bid		S175
	sirolimus	10 mg sd	3.31	cyclosporin A	300 mg sd		S176
	tolvaptan	30 mg sd	5.40	ketoconazole	200 mg qd		S75
	topotecan	1mg/m^2 sd	1.76	elacridar (GF120918)	1000 mg sd		S177
BCRP	**imatinib**	400 mg qd	***	(PGx)		Ctrough/Dose: ×1.36 [421CC (N = 42) vs 421CA/AA (N = 25)]	S178
	rosuvastatin	20 mg sd	1.55	(PGx)		Caucasian [421CC (N = 24) vs 421CA (N = 5)]	S179
		10 mg sd	2.64	(PGx)		Chinese [421CC (N = 10) vs 421AA (N = 10)]	S180
		20 mg sd	2.44	(PGx)		Finnish [421CC (N = 16) vs 421AA (N = 4)]	S181
		20 mg sd	1.78	(PGx)		Chinese [421CC (N = 7) vs 421CA or AA (N = 7)]	S182
	sulfasalazine	2000 mg sd	5.08	(PGx)		Japanese (NAT2: rapid acetylator) [421CC (N = 5) vs 421AA (N = 3)]	S183
		1000 mg sd	2.37	(PGx)		(no information about ethnicity) [421CC (N = 9) vs 421CA (N = 5)]	S184
OATP1B1, OATP1B3	**asunaprevir**	200 mg sd	14.8	rifampicin	600 mg sd		S185
	atorvastatin	40 mg sd	8.51	rifampicin	600 mg sd	Chinese (*SLCO1B1*: c.521TT)	S186
		50 mg sd	8.57	rifampicin	600 mg sd	cocktail study	S187
		33 mg sd	12.0	rifampicin	600 mg sd	cocktail study	S188
	bosentan	500 mg bid	1.97	cyclosporin A	300 mg bid		S189
	docetaxel	75 mg/m^2 sd	7.32	cyclosporin A	15 mg/kg sd		S190
	fexofenadine	180 mg sd	***	(PGx)		CLnr: ×0.81, Caucasian [*SLCO1B1*521TT (N = 10) vs 521TC (N = 8)]	S191
	glibenclamide	1.25 mg sd	2.18	rifampicin	600 mg sd (i.v.)		S192
	nateglinide	90 mg sd	1.81	(PGx)		Chinese [*SLCO1B1*521TT (N = 11) vs 521TC (N = 4)]	S193
		120 mg sd	1.34	(PGx)		Chinese [*SLCO1B1*521TT (N = 9) vs 521TC or CC (N = 13)]	S194
	paclitaxel	60 mg/m^2 sd	8.5	cyclosporin A	15 mg/kg sd		S195
	pitavastatin	1 mg sd	5.70	rifampicin	600 mg sd		S196
		10 mg sd	4.23	rifampicin	600 mg sd	cocktail study	S187
		0.2 mg sd	5.05	rifampicin	600 mg sd		S197
		4 mg sd	5.28	rifampicin	600 mg sd		S198
	pravastatin	20 mg sd	2.27	rifampicin	600 mg sd		S199
		33 mg sd	4.64	rifampicin	600 mg sd	cocktail study	S188
	repaglinide	0.1 mg sd	2.60	rifampicin	600 mg sd		S197
	rosuvastatin	5 mg sd	4.37	rifampicin	600 mg sd		S196
		25 mg sd	4.59	rifampicin	600 mg sd	cocktail study	S187
		5 mg sd	4.67	rifampicin	600 mg sd		S200
	simvastatin acid	40 mg sd (simvastatin)	3.21	(PGx)		Caucasian [*SLCO1B1*521TT (N = 16) vs 521CC (N = 4)]	S201
OAT1, OAT3	**adefovir**	10 mg sd	2.09	probenecid	750 mg sd		S202
	cefaclor	500 mg sd	2.14	probenecid	500 mg bid		S203

	ceftizoxime	1000 mg sd (i.v.)	1.59	probenecid	1000 mg sd		S204
	famotidine	20 mg sd	1.81	probenecid	1500 mg (total) md	1000 mg of probenecid 2h before, 250 mg 1h before and 250 mg simultaneously with famotidine dosing	S205
	furosemide	40 mg sd (i.v.)	3.12	probenecid	1000 mg sd		S206
		80 mg sd	2.68	probenecid	1000 mg sd		S207
	ganciclovir	1000 mg tid	1.55	probenecid	500 mg qid		S208
	methotrexate	200mg/m^2 sd	***	probenecid	500 mg (p.o.), 500 mg (i.v.) or 1000 mg (i.v.) sd	CLp: ×0.64	S209
	oseltamivir carboxylate	75 mg qd or q48h (oseltamivir)	***	probenecid	500 mg qid	CLss/F:× 0.67	S210
		150 mg sd (oseltamivir)	2.52	probenecid	500 mg qid		S211
	bumetanide	200 mg/h (i.v.)	***	probenecid	1000 mg sd (i.v.)	Css:× 2.92	S212
	ciprofloxacin	200 mg sd (i.v.)	1.74	probenecid	3000 mg (total) md	500 mg probenecid at 10 h and 1000 mg at 2 h before the end of the ciprofloxacin infusion, and 500 mg at 4 h, 10 h and 16 h after the end of the ciprofloxacin infusion	S213
		200 mg sd (i.v.)	1.75	probenecid	3000 mg (total) md	500 mg probenecid at 10 h and 1000 mg at 2 h before the end of the ciprofloxacin infusion, and 500 mg at 4 h, 10 h and 16 h after the end of the ciprofloxacin infusion	S214
	fexofenadine	180 mg sd	1.75	probenecid	1000 mg bid		S215
		120 mg sd	1.69	probenecid	1000 mg bid		S167
	zidovudine	100 mg qd	1.57	probenecid	500 mg bid		S216
		2 mg/kg tid	2.06	probenecid	500 mg bid		S217
MATE1, MATE2-K, OCT2	**metformin**	250 mg qd	1.46	cimetidine	400 mg bid		S218
		500 mg sd	1.54	cimetidine	400 mg bid	*SLC22A2*:808GG (N = 6)	S219

Note. The table is prepared to provide examples and not intended to be an exhaustive list. Other elimination pathways may also contribute to the elimination of the substrates listed and should be considered when assessing the drug interaction potential. .A list of references for the tables are provided in the appendix.

[a] Multiple doses were given for qd, bid and tid. Abbreviation sd and md refers to single dose and multiple dose, respectively.

[b] If AUCR of substrate is not available in the literature, other PK parameter we selected is shown in the comment column. Ctrough/Dose: dose-normalized trough concentration in plasma, CLnr: non-renal clearance, CLp: plasma clearance, CLss/F: steady-state total clearance divided by bioavailability, Css: steady-state plasma concentration.

[c] (PGx) represents the ratio of the AUC of substrate in subjects with specific type of allele to that in subjects with wild type allele. Target allele, subject number and ethnicity (if available) are described in the comment column.

[d] Because most of the P-gp substrate is also a substrate of CYP3A and BCRP and these inhibitors can inhibit not only P-gp but CYP3A and BCRP, it should be cautious that relative contribution of P-gp inhibition to the overall AUC increase of substrate has not been clarified.

Table 5
Examples of transporter-mediated pharmacokinetic drug interactions for inhibitors listed in Japanese guideline.

isoform	inhibitor		concomitantly used substrate			comment[b]	ref.
	name	dose[a]	name	dose[a]	AUCR [b]		
P-gp	**amiodarone**	200 mg qd	digoxin	0.5 mg sd	1.48		S220
		800 mg qd	digoxin	(not reported)	1.68	stable therapy	S221
	carvedilol	6.25 mg bid	digoxin	0.0625–0.25 mg qd	1.57 (male) 1.24 (female)	stable therapy	S222
	clarithromycin	500 mg bid	digoxin	0.25 mg sd	1.47		S223
		250 mg bid	digoxin	0.75 mg sd	1.64		S224
		500 mg bid	digoxin	0.5 mg sd	1.57		S225
	itraconazole	200 mg qd	digoxin	0.5 mg sd	1.68		S226
	lapatinib	1500 mg qd	digoxin	0.5 mg sd	1.63		S227
	lopinavir/ritonavir	400/100 mg bid	digoxin	0.5 mg sd	1.81	cocktail study	S228
	quinidine	62.5 mg sd	digoxin	0.5 mg sd	3.28		S229
		600 mg bid	digoxin	0.4 mg qd	2.65		S166
		(not reported)	digoxin	(not reported qd)	1.77		S230
	ritonavir	300 mg bid	digoxin	0.5 mg sd	1.86		S231
		400 mg bid	digoxin	0.5 mg sd	1.47		S232
	saquinavir/ritonavir	1000mg/100 mg bid	digoxin	0.5 mg sd	1.68		S233
	telaprevir/ritonavir	750 mg tid	digoxin	0.5 mg sd	1.81		S234
	verapamil	80 mg bid/tid	digoxin	0.25 mg bid	1.50		S235
	azithromycin	250 mg qd	fexofenadine	60 mg bid	1.72		S236
	cyclosporin A	(not reported)	digoxin	(not reported)	***	plasma CL:× 0.47	S237
BCRP	**curcumin**	2 g sd	sulfasalazine	2 g sd	3.23		S238
	eltrombopag	75 mg qd	rosuvastatin	10 mg sd	1.55		S239
OATP1B1, OATP1B3	**atazanavir/ritonavir**	300mg/100 mg qd	rosuvastatin	10 mg sd	3.13		S240
	clarithromycin	500 mg bid	rosuvastatin	25 mg sd	1.56	cocktail study	S187
	cyclosporin A	75–200 mg bid	rosuvastatin	10 mg qd	7.08		S241
	erythromycin	500 mg qid	pitavastatin	4 mg sd	2.79		S242
		500 mg qid	atorvastatin	10 mg sd	1.33		S243
	lopinavir/ritonavir	400mg/100 mg bid	rosuvastatin	20 mg qd	2.08		S244
	rifampicin	600 mg sd	rosuvastatin	5 mg sd	4.09		S196
		600 mg sd	rosuvastatin	25 mg sd	4.59	cocktail study	S187
		600 mg sd	rosuvastatin	5 mg sd	4.67		S200
	simeprevir	150 mg qd	rosuvastatin	10 mg sd	2.81		S245
OAT1, OAT3	**probenecid**	1500 mg sd	benzylpenicillin	400000 U sd	3.27		S202
MATE1, MATE2-K, OCT2	**cimetidine**	400 mg bid	metformin	250 mg qd	1.46		S218
		400 mg bid	metformin	500 mg sd	1.54	*SLC22A2*:808GG (N = 6)	S219
	dolutegravir	50 mg bid	metformin	500 mg bid	2.45		S246
	(pyrimethamine)[c]	50 mg sd	metformin	250 mg sd	1.35		S247
		50 mg sd	metformin	750 or 500 mg sd	2.70		S248
	trimethoprim	200 mg bid	metformin	500 mg tid	1.37		S249
	vandetanib	800 mg sd	metformin	1000 mg sd	1.74		S250

Note. The table is prepared to provide examples and not intended to be an exhaustive list. Other elimination pathways may also contribute to the elimination of the substrates listed and should be considered when assessing the drug interaction potential. A list of references for the tables are provided in the appendix.
[a] Multiple doses were given for qd, bid and tid. Abbreviation sd and md refers to single dose and multiple dose, respectively.
[b] If AUCR of substrate is not available in the literature, other PK parameter we selected is shown in the comment column.
[c] Drugs in parenthesis are not approved in Japanese market currently.

The United States FDA selected the drugs that satisfied the following criteria: AUCR is ≥ 2 in clinical DI studies with verapamil or quinidine, *in vitro* transport by P-gp expression systems has been confirmed, and drugs are not extensively metabolized. In addition to these conditions (verapamil (80 mg): $[I]_g$ (the expected maximum concentration [maximum single dose of inhibitors/250 mL] of the investigational drug in the lumen side of the gastrointestinal tract) divided by half-maximal inhibitory concentration (IC50) = 125 [3.14–11,700], quinidine (200 mg): $[I]_g$/IC50 = 563 [44.0–12,300] (the geometric mean [range] of $[I]_g$/reported K_i or IC50 values for the transport of typical *in vitro* substrates shown in Table 2–1 in the Japanese guideline was used)), cyclosporin A and ketoconazole also have strong inhibition potencies against P-gp in the small intestine *in vivo* based on the static model (Fig. 2–3 in the Japanese guideline) (cyclosporin A (ciclosporin) [200 mg]: $[I]_g$/IC50 = 442 [108–2290], ketoconazole [400 mg]: $[I]_g$/IC50 = 1690 [475–7170] (the geometric mean [range] of $[I]_g$/reported K_i or IC50 values for the transport of typical *in vitro* substrates shown in Table 2–1 in the Japanese guideline was used)). Thus, when the reported AUCR of a substrate drug was $\geq$2 in clinical DI studies with cyclosporin A and ketoconazole, it was added to Table 2–3 in the Japanese DI guideline (Table 4 in this review).

In the case of topotecan, a previous study indicated that its AUCR was 1.76 when elacridar (GF120918) was co-administered [58]. Elacridar is considered to be a dual potent inhibitor of P-gp and BCRP (P-gp: $[I]_g$/IC50 = 106,000 [16,100–455,000], BCRP: $[I]_g$/IC50 = 8480 [5300–14,200] at the dose of 1000 mg (the geometric mean [range] of $[I]_g$/reported K_i or IC50 values for the transport of typical *in vitro* substrates shown in Table 2–1 in the Japanese guideline was used)). Though we cannot conclude the relative importance of P-gp and BCRP in the clinical DI case with elacridar, topotecan was included as a potential substrate of P-gp in Table 2–3 in the Japanese DI guideline (Table 4 in this review). Cyclosporin A is also thought to inhibit intestinal BCRP ($[I]_g$/IC50 = 99.3, 142 at the dose of 200 mg ($[I]_g$/reported K_i or IC50 values for the transport of typical *in vitro* substrates shown in Table 2–1 in the Japanese DI guideline was used)). At present, there are few drugs for which the relative contribution of P-gp and BCRP in the intestine to the suppression of intestinal absorption has been quantitatively identified,

and we have little knowledge about the inhibition potency of P-gp inhibitor drugs for BCRP. Thus, we should be careful about the interpretation of clinical DI outcomes with P-gp inhibitor drugs.

In the interpretation of AUCR values for each P-gp-mediated DI case, we must pay attention to the evidence in which most of the drugs (except digoxin, fexofenadine, and dabigatran etexilate) are metabolized by CYP3A and all of the studied inhibitor drugs can inhibit CYP3A in the intestine and the liver. Currently, the relative contribution of CYP3A and P-gp to the overall effect on the AUCR of affected drugs cannot be clearly separated, and these AUC increases are thought to be caused by the inhibition of both CYP3A and P-gp.

Digoxin has most often been used as a probe for P-gp in clinical DI studies because it is mainly excreted into urine without any extensive metabolism [59]. However, the bioavailability of digoxin is relatively high (about 70%), partly depending on the dosage form, which means that the small margin of AUC increase is caused only by the inhibition of intestinal P-gp (maximum AUCR ~ 1.4 (=1/0.7)). In some DI cases, renal clearance of digoxin was also decreased, suggesting that the role of P-gp-mediated renal efflux in the AUC increased [60]. However, a separation of these contributions has not yet been clearly determined because of the lack of clinical information.

Fexofenadine is a nonmetabolized type of P-gp substrate and its pharmacological effect is relatively mild (histamine H2 receptor antagonist) compared with other P-gp probe drugs. Moreover, the margin of AUC increase caused by intestinal P-gp inhibition is relatively high (bioavailability = 33% (product information: Hoechst Marion, Roussel, Laval, QC, Canada)). However, it is recognized by multiple uptake and efflux transporters such as OATP1Bs, OATP2B1, OAT3, MRP2, MRP3, and MATEs [60–64]. Thus, before clinical DI studies at least, the inhibitory effects of drugs for the fexofenadine transport, mediated by the above-mentioned known transporters must be checked *in vitro* for the accurate prediction of P-gp-mediated DI risks with fexofenadine.

On the other hand, dabigatran etexilate is a prodrug that is metabolized by serum esterase to dabigatran. Previous reports indicate that dabigatran etexilate is a good substrate of P-gp, but not dabigatran, and that dabigatran etexilate was confirmed to be a nonsubstrate of OATPs, OCTs, OATs, MRP2, and BCRP [65]. Because the bioavailability of dabigatran etexilate is about 7%, it enables the sensitive catch of the inhibition potency of inhibitor drugs on intestinal P-gp. However, few clinical DI studies with dabigatran etexilate have been published, so the further accumulation of clinical DI examples is needed to compare the DI prediction performance of dabigatran etexilate with that of other P-gp probes.

4.1.2. Substrates of BCRP

Similar to P-gp, BCRP can also efflux various types of compounds and it is also expressed in multiple tissues and barriers. Pharmacogenetic studies indicated that BCRP contributes to the suppression of intestinal absorption of various drugs such as sulfasalazine and rosuvastatin. Moreover, though direct clinical evidence demonstrating the importance of BCRP in other organs is very limited at this moment, BCRP plays a role in biliary excretion of troglitazone sulfate, renal excretion of bile acids and transplacental transport of glyburide.

There is no BCRP-selective inhibitor among the approved drugs at the moment. The United States FDA selected the drugs that satisfied the following criteria: AUCR is ≥ 2 with pharmacogenetic alteration in subjects with *ABCG2* c.421C > A and *in vitro* transport by BCRP expression systems has been confirmed. Several *in vitro* experiments supported the decreased function of mutated BCRP with *ABCG2* c.421C > A [66,67]. Because the allele frequency of c.421C > A is about 32% in the Japanese population, a pharmacogenetic study can be designed to understand the impact of the decrease in BCRP function on the pharmacokinetics of affected drugs. Rosuvastatin and sulfasalazine are selected as typical BCRP substrates, both in the lists of the United States FDA and Japanese DI guidelines. Rosuvastatin is a nonmetabolized type of statin and is mainly excreted into bile and partly excreted into the urine in an unchanged form. Multiple transporters such as OATP1Bs, Na^+-taurocholate cotransporting polypeptide (NTCP), P-gp, MRP2, and OAT3 are involved in the regulation of rosuvastatin pharmacokinetics [68–70]. Thus, it is difficult to identify the major cause of DIs only from clinical DI outcomes; *in vitro* experimental results should also be considered in parallel.

For example, cyclosporin A is thought to be an inhibitor of intestinal BCRP, and co-administration of cyclosporin A led to a significant increase in the plasma AUC of rosuvastatin [71]. However, previous reports clearly indicate that the major cause of the DI between rosuvastatin and cyclosporin A is the inhibition of hepatic OATP1B transporters by cyclosporin A, though BCRP inhibition also partly contributes to its AUC increase [72,73]. As for sulfasalazine, because its bioavailability is about 7%, it is expected sensitively catch the functional change of intestinal BCRP. This is supported by a previous clinical result in which plasma AUC of sulfasalazine in subjects with *ABCG2* c.421C > A is about 5-fold higherthan subjects with the wild-type allele [74]. Conversely, the aqueous solubility of sulfasalazine shows that it is practically insoluble and largely depends on pH, while its clinical dose is relatively high. Thus, the fraction of the dose absorbed from the intestinal wall may depend on the dose of sulfasalazine. In addition, because the number of examples is very small at this moment, imatinib is also listed in the Japanese DI guideline because its trough plasma concentration normalized by dose was significantly larger in subjects with *ABCG2* c.421C > A, though the AUCR was not available [75].

4.1.3. Substrates of OATP1B1/OATP1B3

OATP1B1/1B3 are exclusively expressed on the basal membrane of hepatocytes and are responsible for the hepatic uptake of substrate drugs. Because of the broad substrate specificities of OATP1B1/1B3, many types of example drugs are listed in the Japanese DI guideline. The United States FDA selected the drugs when the following criteria were satisfied: AUCR is ≥ 2 in clinical DI studies with a single dose of rifampicin or cyclosporin A or with pharmacogenetic alteration in subjects with *SLCO1B1* c.521T > C, and the *in vitro* transport by OATP1B1 or OATP1B3 expression systems has been confirmed. Rifampicin and cyclosporin A have been confirmed to be potent clinically relevant OATP1B inhibitors from *in vitro* inhibition studies (rifampicin [600 mg]: $[I_{u,in,max}]$ (the expected maximum concentration of the inhibitor at the inlet to the liver adopted by the Japanese DI guideline)/IC50 = 5.55 [1.19–24.4] for OATP1B1, 1.11 [0.914–53.2] for OATP1B3; cyclosporin A [200 mg]: $[I_{u,in,max}]$/IC50 = 4.85 [0.740–63.8] for OATP1B1, 4.83 [0.933–37.9] for OATP1B3 (the geometric mean [range] of $[I_{u,in,max}]$/reported K_i or IC50 values was used when estradiol-17β-glucuronide was used as a substrate in transporter-expression systems)).

OATP1B1/1B3 substrates, which were selected by the United States FDA, are listed in the Table 2–3 in the Japanese DI guideline (Table 4 in this review), but danoprevir is only listed in the United States FDA table simply because it has not been approved in Japan. Various types of HMG-CoA reductase inhibitors (statins) are listed because all the acid forms of statins are confirmed to be substrates of OATP1B1/1B3 *in vitro* [73]. Among these statins, pitavastatin, rosuvastatin, and pravastatin are excreted into bile mostly in an unchanged form, while atorvastatin and fluvastatin are extensively metabolized by CYP3A and CYP2C9, respectively, after their hepatic uptake via OATP1Bs. Among the listed drugs, some of them are subsequently metabolized by P450s; thus, the impact on their pharmacokinetics should be taken into consideration in the

interpretation of DI outcomes. Watanabe et al. have shown that *in vivo* hepatic clearances of four types of statins are well predicted from *in vitro* uptake clearance in human hepatocytes rather than from *in vitro* metabolic clearance with human liver microsomes, suggesting that OATP1B1/1B3-mediated hepatic uptake is a rate-determining process of hepatic clearance even for metabolized type of statins [76]. A previous microdosing clinical DI study with atorvastatin further supported its uptake-limited hepatic clearance *in vivo* in humans because the plasma AUC of parent atorvastatin was greatly increased by the oral administration of rifampicin (OATP1Bs inhibitor), while it was not changed by the intravenous administration of itraconazole (hepatic CYP3A inhibitor) [77]. Fluvastatin is now qualified as a listed drug because a recent DI study showed that the AUCR of fluvastatin is 2.4 by single oral dose of rifampicin (600 mg) and this is almost to the same as those of pitavastatin and rosuvastatin [78].

In the interpretation of clinical DI results, we must pay attention to the fact that statins are also recognized by multiple transporters other than OATP1Bs. For example, pitavastatin is a substrate of P-gp, MRP2, and BCRP [79], though the contribution of intestinal BCRP to the suppression of intestinal absorption of pitavastatin was considered to be minor because of its high bioavailability. In the case of rosuvastatin, the partial contribution of NTCP to the hepatic uptake was reported [68], and it is also a substrate of P-gp, MRP2, and BCRP [69]. Pravastatin is thought to be mainly excreted into bile via MRP2 [80]. Moreover, these two statins are partially (~30%) eliminated from the kidney mainly via OAT3.

Other than statins, several NS3/4A protease inhibitors for the treatment of hepatitis C are also known to be substrates of OATP1Bs and some DI cases have recently been reported. AUCRs of simeprevir, grecaprevir, and grazoprevir were reported to be 6.2, 8.6, and 8.4 when rifampicin (600 mg, 300 mg, and 200 mg, respectively) was orally co-administered [81]. The number of OATP1B substrate drugs has been increasing and we must continuously collect information on the pharmacokinetic properties of newly approved drugs. For instance, pemafibrate, a selective PPARα modulator first approved in Japan, is a substrate of OATP1Bs according to the package insert, and co-administration of rifampicin (600 mg) and cyclosporin A (600 mg) greatly increased the plasma AUC of pemafibrate 11- and 14-fold, respectively; thus, these are designated as contraindicated drugs.

4.1.4. Substrates of OAT1/OAT3

OAT1 and OAT3 are expressed on the basal membrane of renal proximal tubular epithelial cells and play important roles in the renal secretion of anionic drugs. The United States FDA selected the drugs when the following criteria were satisfied: the AUCR is $\geq$ 1.5 in clinical DI studies with probenecid, the fraction excreted into the urine in an unchanged form is $\geq$ 0.5, and the *in vitro* transport by OAT1 or OAT3 expression systems has been confirmed. In the drug list of the Japanese DI guideline (Table 2-3), some drugs (bumetanide, ciprofloxacin, fexofenadine, and zidovudine) were newly added to the list of the United States FDA's website because previous clinical reports indicated that the AUCR (or steady-state plasma concentration (only for bumetanide)) of these drugs was $\geq$1.5 on co-administration of probenecid (probenecid [1000 mg]: $[I_{u,max}]/IC50 = 0.14–6.1$ for OAT1, 0.69–29 for OAT3 [the range of reported K_i or IC50 values was used]). As for fexofenadine, though its fraction excreted into urine is < 0.5 (12%) and it is also a substrate of hepatic OATP1B transporters [61,63], the functions of OAT1 and OAT3 can be directly evaluated from its renal clearance, which is calculated by dividing the cumulative amount of drugs excreted unchanged in the urine by blood AUC. So, the second criterion by the United States FDA is not necessarily important to evaluate the change in the functions of OAT1 and OAT3 once renal clearance of drugs is quantified. The same is true for pravastatin and rosuvastatin, 30% of which are excreted unchanged into urine via OAT3.

Regarding penicillin G, a previous report supported the claim that it can also meet the above-mentioned criteria as an *in vivo* OAT3 probe substrate because the plasma concentration of penicillin G was increased 2.1-fold by the oral co-administration of 750 mg of probenecid [82]. This quantitative DI information was not available when the tables were being originally created for the Japanese guideline; thus, penicillin G is also qualified as an *in vivo* OAT3 probe substrate in the review.

In general, substrate specificities of OAT1 and OAT3 are different. OAT1 preferentially accepts low molecular weight and hydrophilic compounds as substrates compared with OAT3 [83]. The molecular properties of OAT3 substrates resemble those of hepatic OATP1B transporters. The relative contribution of OAT1 and OAT3 to the uptake of listed drugs into proximal tubular epithelial cells is of great variety. Based on several methods reported previously to quantify their contributions [84,85], adefovir, ganciclovir, and *p*-aminohippurate (PAH) are selective substrates of OAT1, whereas penicillin G, bumetanide, ciprofloxacin, and oseltamivir carboxylate are selective substrates of OAT3. So, it is noted that the selection of substrate drugs from Tables 2–3 in the Japanese DI guideline (Table 4 in this review) depends on the putative target transporter for renal DIs.

4.1.5. Substrates of OCT2/MATEs

OCT2 is expressed on the basal (blood) side of renal epithelial cells, while MATEs are expressed on the apical (urine) side. The cooperative functions of OCT2 and MATEs in the kidney partly realize the efficient transcellular transport of various organic cations. The United States FDA selected only one drug, metformin, because it is a well-established substrate of the cationic transport system.

Metformin is well-known to be mainly excreted into the urine by active secretion mediated by OCT2/MATEs. Clinical evidence, such as DI and pharmacogenetic studies, as well as animal experiments supported the importance of OCT2/MATEs in the renal clearance of metformin *in vivo* [86–88].

4.2. Notes for the selection of in vivo typical inhibitors of transporters (Table 5)

As for transporter inhibitors, the United States FDA also showed similar types of drug lists on their website (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2); a part of the inhibitor drugs for each transporter is different from those in the Japanese DI guideline (Table 2–4 in the guideline).

4.2.1. Inhibitors of P-gp

Many drugs have been nominated as *in vivo* typical inhibitors of transporters in the tables of both the United States FDA's website and Japanese DI guideline, though some of the listed drugs are not identical between these tables. The United States FDA selected the drugs when the following criteria were satisfied: the AUCR of digoxin is $\geq$ 2 in clinical DI studies and the *in vitro* inhibition of P-gp has been confirmed. However, according to the drug-interaction database, DIDB (http://www.druginteractioninfo.org), the AUCR of digoxin is within the range of 1.5–2.0 in co-administration as with most of the listed drugs (Table 5). For the practical use of these inhibitors, we should pay attention to the evidence in which most of these inhibitors also inhibit CYP3A; thus, even if the plasma concentration of a drug is increased by co-administration of the listed inhibitors, the major mechanism of DIs cannot be simply determined using clinical DI studies.

Compared with the list of the United States FDA's website, cyclosporin A and azithromycin were also listed in Table 2-4 in the Japanese DI guideline (Table 5 in this review). A previous case report indicated that cyclosporin A decreased plasma clearance of digoxin 0.47-fold and cyclosporin A potently inhibits P-gp in *in vitro* experiments as mentioned above [89]. Other clinical data also strongly suggested that cyclosporin A works as a clinically relevant P-gp inhibitor. However, the interpretation of the clinical DI outcome with cyclosporin A must be made with caution because it also inhibits intestinal BCRP and CYP3A, and hepatic OATP1B1/OATP1B3. As for azithromycin, though a clinical DI study with digoxin is not available at the moment, the *in vitro* inhibition potency of azithromycin was strong enough to inhibit intestinal P-gp in humans ($[I]_g/IC50 = 61.2$ at 250 mg dose) [90], and a previous report indicated that azithromycin significantly increased the plasma AUC of fexofenadine 1.7-fold [90].

Although propafenone is only listed in the United States FDA table but not in the Japanese guideline, a previous clinical DI study showed that the plasma concentration of digoxin was increased 1.8-fold by co-administration of propafenone (300 mg/8 h for 3 days) [91] and the *in vitro* inhibition potency has been confirmed ($[I]_g/IC50 = 173, 517$ at 300 mg dose) [92]. Thus, propafenone can also be qualified as a P-gp inhibitor drug. Ranolazine, dronedarone and tipranavir/ritonavir are not included in the list in the Japanese guideline simply because they have not been approved in Japan.

4.2.2. Inhibitors of BCRP

The United States FDA selected the drugs when the following criteria were satisfied: the AUCR of sulfasalazine is ≥ 1.5 in clinical DI studies and the *in vitro* inhibition of BCRP has been confirmed. However, only curcumin meets those criteria because clinical DI studies with sulfasalazine are very rare at the moment. The disadvantage of the use of curcumin for a DI study is that a large amount of dose (2 g) is required to inhibit BCRP in humans [93]. The United States FDA also considers cyclosporin A and eltrombopag as BCRP inhibitors because they increase the plasma AUC of rosuvastatin 6.1-fold and 1.6-fold, respectively [71,94]. However, it should be noted that a major mechanism of DI between rosuvastatin and cyclosporin A is considered to be the inhibition of hepatic OATP1B1/OATP1B3 rather than the inhibition of intestinal BCRP [73]. Thus, cyclosporin A is not included in the list of the Japanese guideline. A recent paper suggested that the clinical dose of eltrombopag may also partly inhibit hepatic OATP1B1/OATP1B3 [95]. Therefore, there is no good specific inhibitor for BCRP at the moment. To check whether the intestinal absorption of a drug is dominated by BCRP, another option is to compare its plasma concentrations in subjects with the *ABCG2* c.421C > A mutation with those in subjects with wild-type *ABCG2*, as mentioned above.

4.2.3. Inhibitors of OATP1B1/OATP1B3

The United States FDA selected the drugs when the following criteria were satisfied: the AUCR of one of the clinical substrates in the United States FDA list is ≥ 2 in clinical DI studies and the *in vitro* inhibition of OATP1B1 and/or OATP1B3 has been confirmed. Among these drugs, rifampicin has been frequently used in OATP1B-mediated clinical DI studies because its pharmacological effect is relatively mild among the listed OATP1B inhibitors. Because rifampicin also works as a strong inducer of P-gp, some P450 isoenzymes (CYP2C9, 2C19, 2B6, and 3A) whose genes are regulated by the nuclear receptor PXR, and possibly OATP1B1 [96–98] (some controversial results have also been published [99–102]), repeated dosing of rifampicin must be avoided and a single dose of rifampicin (typically 600 mg) should be used to evaluate the impact of hepatic OATP1B transporters on the pharmacokinetics of affected drugs. All the listed OATP1B inhibitors have an inhibition potency for intestinal P-gp and CYP3A to some extent, so we should be careful in clinical DI data interpretation. Although gemfibrozil has not been approved in Japan and it is not listed in the Japanese guideline, it mildly increased the plasma AUC of various types of statins 1.1–2.0-fold, except cerivastatin (5.6-fold) [103] because of a combination of mechanism-based inhibition of hepatic CYP2C8 by gemfibrozil glucuronide and inhibition of hepatic OATP1B transporters by both gemfibrozil and its glucuronide [25].

4.2.4. Inhibitors of OAT1/OAT3

Probenecid is the only drug listed in the Japanese guideline that is a potent inhibitor for both OAT1 and OAT3. K_i values of probenecid for OAT1 (4.0 μM) and OAT3 (3.5 μM) are reported to be almost the same [82], so probenecid is considered to inhibit both OAT1 and OAT3 to the same extent in humans. Thus, the relative contribution of OAT1 and OAT3 to the renal uptake of OAT1/OAT3 substrate drugs cannot be determined only from clinical DI studies with probenecid. A previous report demonstrated that 750 mg of probenecid significantly decreased the renal clearance of adefovir (an OAT1-selective substrate) and penicillin G (an OAT3-selective substrate) by 82% and 54%, respectively, and the dose-dependent change in their renal clearances could be reasonably explained by *in vitro* K_i values for OAT1 and OAT3 and the average unbound plasma concentration of probenecid at each dose [82].

On the other hand, the United States FDA selected two additional drugs, PAH and teriflunomide as OAT1/OAT3 inhibitors based on the following criteria: the AUCR of one of the clinical substrates in the United States FDA table is ≥ 1.5 in clinical DI studies and the *in vitro* inhibition of OAT1 and/or OAT3 has been confirmed. A previous report demonstrated that PAH meets the above-mentioned criteria as an *in vivo* relatively selective inhibitor for OAT1 because a large difference in K_i values for OAT1 and OAT3 was confirmed *in vitro* and the plasma concentration of adefovir was increased by 1-h continuous infusion of PAH at the rate of 120 mg/min, and a dose-dependent change in its renal clearance could be explained by *in vitro* K_i values for OAT1 and average unbound plasma concentration of PAH at each dose [82]. This quantitative DI information was not available at the time the tables were being originally created for the Japanese guideline; thus, PAH is useful for the selective inhibition of OAT1 in the human kidney. However, unexpectedly, PAH clearly increased the renal clearance of penicillin G in a dose-dependent manner, which might be caused by the inhibition of the reabsorption process of penicillin G via unidentified transporter(s) [82].

Repeated dosing of teriflunomide increased the plasma AUC of cefaclor 1.5-fold, suggesting that it inhibits renal OAT3 in humans [104]. On the other hand, an interpretation of clinical DI results should be made with caution because teriflunomide may also inhibit CYP2C8, BCRP, and OATP1B1/OATP1B3 because plasma AUCs of repaglinide and rosuvastatin were increased 2.3- and 2.5-fold, respectively [104]. *In vitro* IC50 values of teriflunomide for BCRP, OATP1B1, and OAT3 were 0.146, 7.4, and 1.03 μM, respectively, resulting in $[I]_g/IC50 = 1420$ (for BCRP), $[I_{u,in,max}]/IC50 = 0.231$ (for OATP1B1 (unbound fraction is set as 0.01)) and $[I_{u,max}]$ (the maximum unbound concentration of the inhibitor in the blood)/IC50 = 1.63 (for OAT3 (unbound fraction is set as 0.01)) at 14 mg dose [104].

4.2.5. Inhibitors of OCT2/MATEs

The listed inhibitors for OCT2/MATEs in the Japanese guideline and FDA's website are almost the same. The United States FDA selected the drugs when the following criteria were satisfied: the AUCR of metformin is ≥ 1.5 in clinical DI studies and the *in vitro* inhibition of OCT2 and/or MATEs has been confirmed. In Table 5, the inclusion criteria were met for all the listed drugs. Isavuconazole and ranolazine are not included in the list in the Japanese guideline because they have not been approved in Japan.

The reason why pyrimethamine is included in the Japanese guideline is that it is well-validated as a MATEs-selective inhibitor. *In vitro* inhibition assay of pyrimethamine for renal cation transport systems revealed its highly selective inhibition of MATEs (K_i for MATE1: 0.151 [0.0193–93.5] μM, MATE2-K: 0.136 [0.01–1.50] μM (geometric mean [range] of reported K_i or IC50 values in transporter-expression systems)) compared with OCT2 (K_i = 6.17 [0.61–160] μM). A similar tendency is also observed for cimetidine (K_i for OCT2: 59.9 [1.8–1650] μM, MATE1: 2.15 [0.093–16.3] μM, MATE2-K: 8.14 [2.1–46.6] μM), trimethoprim (K_i for OCT2: 61.4 [6.9–1330] μM, MATE1: 3.56 [0.51–29.1] μM, MATE2-K: 0.445 [0.03–28.9] μM), and vandetanib (K_i for OCT2: 6.18 [0.4–73.4] μM, MATE1: 0.337 [0.06–1.23] μM, MATE2-K: 0.297 [0.04–1.26] μM), which suggests that they also preferentially inhibit MATEs rather than OCT2. Conversely, inhibition potencies of dolutegravir for OCT2 (K_i = 2.12 [0.066–23] μM) and MATEs (K_i for MATE1: 4.99 [3.6–6.34] μM, MATE2-K: 19.4 [9.3–49.3] μM) are similar. However, the unbound maximum plasma concentration of dolutegravir is 0.11 μM at 50 mg dose, which is less than the K_i values for OCT2 and MATEs. Thus, clinical DIs with dolutegravir may not be simply explained by the inhibition of OCT2 and MATEs.

5. Other clinically evident pharmacokinetic DIs

In this review, we have focused on P450 and transporter-mediated DIs, because it is currently difficult systematically to manage the DIs of the other mechanisms. Nevertheless, it is important to know the risks of clinically evident DIs of the other mechanisms. In addition to P450, multiple metabolizing enzymes, including flavin monooxygenase (FMO), monoamine oxidase (MAO), xanthine oxidase (XO), and aldehyde oxidase (AO) [105,106], various esterases and peptidases [107], as well as conjugating enzymes such as UGT [108] and sulfotransferase [109] play important roles in the regulation of drug clearance. Among these, glucuronidation is the most commonly observed metabolizing enzyme next to P450, and it has been elucidated that multiple isoenzymes of UGT are expressed in the liver, small intestine, and kidney [110].

However, the information of DIs on the selectivity of substrates or inhibitors is not fully clarified for UGT compared with those for P450. It has been reported that drugs such as valproic acid [111], lamotrigine [112], zidovudine [113], deferasirox [114], canagliflozin [115], and raltegravir [116] are extensively glucuronidated without phase I metabolism, but the degrees of DI due to UGT inhibition are relatively moderate with AUC changes of less than double for most of these drugs [117] except for a DI between valproic acid and carbapenem, which is described later. However, when these drugs are used in combination with strong inducers, such as rifampicin, evident decreases in AUC have been observed.

When carbapenems, such as panipenem or meropenem, are used in combination with valproic acid, the blood concentration of valproic acid is remarkably reduced, as if the glucuronidation activity is increased [118]. It has been reported that the mechanism of this interaction involves irreversible inhibition of the enzyme that hydrolyzes the valproic acid conjugate and returns it to valproic acid [119,120]. Currently, there are no known drugs that interact with carbapenem by this mechanism other than valproic acid.

It has also been reported that evident pharmacokinetic DIs occur due to fluctuations in absorption [121–123]. Some of these DIs are described in the Japanese guideline.

6. Concluding remarks

Problematic DIs mediated by P450s and transporters are often observed in clinical studies or even post-approval, therefore it is very important systematically to evaluate the risks of such DIs and take the necessary precautions at the right timing. The classification of drugs presented in this study allows for a better understanding of the mechanism or potency for pharmacokinetic DIs and will support efficient drug development and the realization of improved pharmacotherapy in clinical practice. As we have discussed in this review, however, there are still many open issues in this area. Even in the short term after the publication of the Japanese guideline, novel quantitative DI information that was not available at the time the tables were being created has become available such as substrates of OATP1Bs, OAT3, and OCT2/MATEs (pemafibrate, penicillin G, and dofetilide, respectively) or an inhibitor of OAT (PAH). Thus, the tables that were created based on current pharmacokinetic knowledge should be updated appropriately if new information appears in the future. It is also noteworthy that an activity to seek industry–government–academia collaboration to update and maintain the FDA's list has been reported [124]. Individual regulatory standards for the evaluation of DIs have been issued in the EU, Japan, and the US, however, the international council for harmonization of technical requirements for pharmaceuticals for human use (ICH) has started activities to harmonize the evaluation of DIs during drug development (https://www.ich.org/page/multidisciplinary-guidelines). It is expected that the harmonized guidelines will contribute to reducing the uncertainty of development or shortening the development period. Even if the mechanism is uncommon, such as the DI of sorivudine, it is necessary to manage clinically occurring risks meticulously [125]. The clinical significance of DIs should be considered regarding not only the pharmacokinetic impact but also whether the pharmacokinetic changes affect the therapeutic effect or lead to safety concerns. We should use the classification with understanding its benefits and limitations thoughtfully for evaluation and management of all potential DIs.

Glossary

- Investigational drug: A medicinal product or a drug under development that is investigated as to its potential to act as an affecting drug or an affected drug.
- Concomitant drug: When two or more drugs are used, each drug is called a concomitant drug, in the broad sense. In the narrow sense, a concomitant drug is a drug that is added to the basic drug treatment.
- Substrate: A drug that is subject to metabolism or transport by transporters.
- Interacting drug: In pharmacokinetic DIs, a drug that affects the pharmacokinetics of other drugs when administered concomitantly. For instance, in the case of metabolism, the affecting drug may inhibit or induce drug metabolizing enzymes.
- Affected drug: In pharmacokinetic DIs, a drug whose pharmacokinetics is affected by a concomitant drug. For instance, in the case of metabolism, the metabolism of an affected drug may be decreased by inhibition of the drug metabolizing enzymes or increased by induction of the drug metabolizing enzymes by the interacting drug.
- Index drug: A drug that has been demonstrated in multiple clinical studies to have a high specificity for the enzymes and represents the changes in the pharmacokinetics. It needs to be possible to quantify index drugs and show them as having high safety if they are to be used in clinical studies.
- Selective inhibitor, selective substrate: A drug that rather strongly inhibits a specific drug metabolizing enzyme; a drug that is metabolized or transported selectively by a specific drug metabolizing enzyme or transporter.
- Typical inhibitor, typical substrate: A typical inhibitor may inhibit multiple drug metabolizing enzymes or transporters and a typical substrate may be a substrate for multiple drug

metabolizing enzymes or transporters, so that it is not necessarily a selective inhibitor or a selective substrate.

- Strong inhibitor, moderate inhibitor, weak inhibitor: When a drug is considered to increase the AUC of sensitive substrates by ≥ 5-fold (or decrease the CL/F to less than 1/5), the drug is termed a "strong inhibitor"; a drug that is considered to cause an increase in the AUC by ≥ 2-fold but <5-fold (or a decrease in the CL/F to <1/2 but ≥1/5) is termed a "moderate inhibitor"; and a drug that is considered to cause an increase in the AUC by ≥ 1.25-fold but <2-fold (or a decrease in the CL/F to <1/1.25 but ≥1/2) is termed a "weak inhibitor."
- Strong inducer, moderate inducer, weak inducer: A drug that is considered to reduce the AUC of sensitive substrates to ≤1/5 (or increase the CL/F ratio by > 5-fold) is termed a "strong inducer," a drug that is considered to cause a decrease in the AUC to ≤1/2 but >1/5 (or an increase in the CL/F by ≥ 2-fold but <5-fold) is termed a "moderate inducer," and a drug that is considered to reduce the AUC to ≤1/1.25 but >1/2 (or increase the CL/F by ≥ 1.25-fold but <2-fold) is termed a "weak inducer."
- Sensitive substrate, moderate sensitive substrate: A substrate susceptible to pharmacokinetic DIs whose AUC increases by ≥ 5-fold (or decreases the CL/F to <1/5) when co-administered with a "strong inhibitor"; a substrate moderately susceptible to pharmacokinetic DIs whose AUC increases by ≥ 2-fold but <5-fold (or decreases the CL/F to <1/2 but ≥1/5) when co-administered with a "strong inhibitor."

Declaration of competing interest

The authors declare no conflict of interest. The views presented in this article are those of authors and do not necessarily reflect the official position of the Pharmaceuticals and Medical Devices Agency.

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Appendix A. Supplementary references (Tables 1-5)

Supplementary references (Table 1-5) to this article can be found online at https://doi.org/10.1016/j.dmpk.2021.100414.

Author contributions

K.M. and A.H. wrote the original manuscript draft. N.N., Y.O. and K.M. surveyed the data in NDAs and literatures. All authors contributed to the writing, reviewing and editing of the document.

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