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COMMENTARY

An Overview of Transporter Information in Package Inserts of Recently Approved New Molecular Entities

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ABBREVIATIONS

ABC	ATP-binding cassette
ADME	absorption, distribution, metabolism, and excretion
BCRP	breast cancer resistance protein
BSEP	bile salt export pump
DDI	drug-drug interaction
EMA	European Medicines Agency
FDA	Food and Drug Administration
ITC	International Transporter Consortium
MATE	multidrug and toxic compound extrusion
MCT	monocarboxylate transporter
MRP	multi-drug resistance-associated protein
NET	norepinephrine transporter
NCTP	Na^+-taurocholate cotransporting polypeptide
NDA	new drug application
NME	new molecular entity
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
P-gp	P-glycoprotein
PI	package insert
PK	pharmacokinetics
PD	pharmacodynamics
SLC	solute carrier
VMAT	vesicular monoamine transporter

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INTRODUCTION

Transporters are membrane-bound proteins that control the access of endogenous compounds and xenobiotics (drugs) to various sites in the human body. They can influence both drug pharmacokinetics (PK) and pharmacodynamics (PD) by affecting a drug's absorption, distribution, metabolism (via control of access to metabolizing enzymes), and excretion (ADME). Changes in transporter expression or activity either via genetic factors or drug interactions may contribute to variability in drug exposure and response. Several recent publications and scientific meetings have discussed the importance of evaluating transporter-mediated drug interactions during drug development and regulatory review, including the Food and Drug Administration (FDA's) draft drug-drug interaction (DDI) Guidance in 2006, the International Transporter

Consortium (ITC) whitepaper in 2010 (1,2), the Clinical Pharmacology Advisory Committee Meeting in 2010 (3), and more recently a revised FDA's draft DDI Guidance and European Medicines Agency (EMA)'s Scientific Guideline on the Investigation of Drug Interactions in 2012 (4,5). FDA also periodically updates information on the "FDA Drug Development and Drug Interaction" website (6) to provide decision models that outline steps to determine if an *in vivo* transporter-based DDI study should be conducted for an investigational drug based on *in vitro* assessment.

In this commentary, we surveyed package inserts (PIs) of recently approved new molecular entity (NME) drugs (2003–2011) for transporter-related information to discuss the current status of inclusion of transporter information in the PIs. In particular, we compared the number of PIs with transporter information for NMEs approved in 2003–2006 (pre-2006 DDI Guidance) and 2007–2011 (post-2006 DDI guidance) to evaluate if the FDA's 2006 draft DDI Guidance may have influenced the amount of transporter information in new drug applications (NDAs). The location of the transporter information in various sections of the PIs (e.g., Highlights, Dosage and Administration, Drug Interactions, etc.) may reflect the clinical significance of transporter-based DDI in the safe and effective use of a drug. The survey results may also generally reflect recent developments in the area of transporter research and highlight the clinical significance of transporter involvement in drug disposition.

In addition, general principles for effective communication of transporter information within PIs are discussed so that clinically relevant information may be easily located and better understood by the health care practitioners and patients.

METHODS

Package inserts (also referred to as PIs or labeling) for 183 NMEs (excluding biologics) approved by the FDA between 2003 and 2011 were reviewed for transporter-related information. The most recent versions of all PIs available through Drugs@FDA as of March 29, 2012 were reviewed for transporter information, including transporter-related *in vitro* assessments, *in vivo* DDI studies, or both.

RESULTS

General Overview of Transporter Information in NME Package Inserts

Based on our analyses of transporter data retrieved from package inserts (PIs) for 183 NMEs (excluding biologics) approved by the FDA between 2003 and 2011, the following observations were made.

Of the 183 NME PIs, 40% (74/183) included the name of a specific transporter (Supplementary Material Table SI). The ABC (ATP-binding Cassette) superfamily efflux transporter, P-glycoprotein (P-gp/MDR1/ABCB1), was most frequently mentioned in the PIs (86%, 64/74) followed by Organic Anion Transporting Polypeptides (OATPs, 18%, 13/74), Breast Cancer Resistance Protein (BCRP, 15%, 11/74), Organic Cation Transporters (OCTs, 15%, 11/74) and Organic Anion Transporters (OATs, 8%, 6/74). Other specific transporters mentioned included Bile Salt Export Pump (BSEP), Multidrug And Toxic Compound Extrusion Protein (MATE), Monocarboxylate Transporter (MCT), Multi-drug Resistance-associated Protein (MRP), Norepinephrine Transporter (NET), Na^+-Taurocholate Cotransporting Polypeptide (NTCP), System L Transporter, and Vesicular Monoamine Transporter (VMAT2) (Table I). Inclusion of transporter information in the NME PIs increased from 10% in 2003 to 40% in 2006 and to 71% in 2011 (Supplementary Material Figure S1).

Of the 74 NMEs whose PIs included specific transporter names, 78% (58/74) were administered orally, 16% (12/74) intravenously, and the rest via subcutaneous, transdermal or inhalation routes. Inclusion of transporter information in the PIs for NMEs intended for oral administration increased from 15% in 2003 to 60% in 2006 and to 79% in 2011 (Supplementary Material Figure S1).

Of the various therapeutic areas in which NMEs were approved, oncology (28%), neurology/psychiatry (17%), cardiorenal (14%), and antiviral (12%) PIs included transporter information most frequently (Supplementary Material Figure S2).

Of the various sections in a PI formatted under the Physician Labeling Rule (PLR) (7), transporter information was included in Highlights, Dosage and Administration (Section 2), Warnings and Precautions (Section 5), Drug Interactions (Section 7), Clinical Pharmacology (Section 12) and Patient Counseling Information (Section 17). Under Section 12 "Clinical Pharmacology", transporter information was included under sub-sections of Pharmacokinetics (Section 12.3) such as Absorption, Metabolism, Elimination, and Drug Interactions.

Table I lists the specific transporters included in the PIs of the 74 NMEs approved between 2003 and 2011. Drugs associated with each transporter are listed in alphabetical order. The information in Table I is classified based on: (1) NME as a substrate, non-substrate, inhibitor, or non-inhibitor as indicated in its PI (transporter induction data, when available, is noted with superscripts a and b as well as in Footnotes), and (2) Source of the transporter information, i.e. *in vitro* assessments or *in vivo* DDI studies as stated in PIs. It is important to note that for this commentary, an NME was listed as an *in vivo* substrate or inhibitor for a transporter

Table I New Molecular Entities (Approved 2003–2011) Classified as Substrates, Non-Substrates, Inhibitors, or Non-Inhibitors of Transporters Based on Information Included in Their Package Inserts

Transporter	Substrate	Non-substrate	Inhibitor	Non-inhibitor
ABC Transporters				
P-gp or MDR1 (ABCB1)	aliskiren	*abiraterone (and metabolite)*	*abiraterone metabolite*	aliskiren
	alvimopan (and metabolite)	*dalfampridine*	*boceprevir*	*alvimopan (and metabolite)*
	ambrisentan	*degarelix*	*cabazitaxel*[c]	ambrisentan
	bendamustine	*desvenlafaxine*	conivaptan	aprepitant
	boceprevir	*eltrombopag*	*crizotinib*	*clobazam (and metabolite)*
	cabazitaxel	eribulin[d]	darunavir	dabigatran
	clobazam (and metabolite)	*ezogabine*	dronedarone	*dalfampridine*
	crizotinib	fingolimod	etravirine	*degarelix*[b]
	dabigatran etexilate	*gabapentin*	*eribulin*	*desvenlafaxine*
	everolimus	*iloperidone (and metabolite)*	*everolimus*	*ezogabine*
	fidaxomicin (and metabolite)	*lacosamide*	*ezogabine metabolite*	fidaxomicin
	indacaterol	*micafungin*	*ixabepilone*	*fingolimod*[b] *(and metabolite)*
	ixabepilone	*pralatrexate*	lapatinib	*gabapentin*
	lapatinib	*ruxolitinib*	*maraviroc*	*iloperidone*
	lenalidomide	sorafenib	*nilotinib*	*indacaterol*[b]
	linagliptin	*tetrabenazine (and*	*paliperidone*	lacosamide
	maraviroc	*metabolites)*	ranolazine (and metabolite)	lenalidomide
	nilotinib	*vorinostat*	*rifaximin*	linagliptin[d]
	paliperidone		*sorafenib*	lurasidone
	pazopanib		telaprevir	*micafungin*
	posaconazole		*temsirolimus*	*pralatrexate*
	ranolazine		ticagrelor (and metabolite)	prasugrel
	rifaximin		tipranavir[a]	*raltegravir*
	rivaroxaban		tolvaptan	ramelteon
	romidepsin		*vemurafenib*	rivaroxaban
	saxagliptin			roflumilast (and metabolite)
	silodosin			*rotigotine*
	sitagliptin			*rufinamide*
	telaprevir			*ruxolitinib (and metabolite)*
	temsirolimus			saxagliptin[b]
	ticagrelor (and metabolite)			silodosin
	tipranavir			sitagliptin
	tolvaptan			tadalafil
	vemurafenib			tetrabenazine (and metabolites)
				vorinostat
BSEP (ABCB11)	–	–	–	*fingolimod (and metabolite)*
MRP1 (ABCC1)	–	*cabazitaxel*	–	*cabazitaxel*
		lenalidomide		
MRP2 (ABCC2)	*gadobenate*	*cabazitaxel*	*pralatrexate*	*cabazitaxel*
	pralatrexate	fingolimod		*fingolimod (and metabolite)*
		lenalidomide		*indacaterol*[b]
MRP3 (ABCC3)	*pralatrexate*	*lenalidomide*	*pralatrexate*	–
BCRP (ABCG2)	*bendamustine*	*cabazitaxel*	eltrombopag	*fingolimod (and metabolite)*
	eltrombopag	*ixabepilone*	*cabazitaxel*[c]	*indacaterol*
	lapatinib		*lapatinib*	*pralatrexate*
	pazopanib		*rivaroxaban*	*ruxolitinib (and metabolite)*

Table I (continued)

Transporter	Substrate	Non-substrate	Inhibitor	Non-inhibitor
	pralatrexate *rivaroxaban*			
SLC Transporters				
NET (SLC6A2)	*iobenguane*	–	–	–
System L (SLC7A5)	*pregabalin*	–	–	–
NTCP (SLC10A1)	–	–	–	*fingolimod (and metabolite)*
MCT-1 (SLC16A1)	gabapentin	–	–	gabapentin
VMAT2 (SLC18A2)	–	–	–	*tetrabenazine*
OATP (no specific OATP transporter mentioned)	–	gadoxetate	–	–
OATP1B1 or OATP-C (SLCO1B1)	ambrisentan	*eltrombopag* fingolimod *lenalidomide* *pralatrexate*	*dronedarone (and metabolite)* eltrombopag *lapatinib* *pazopanib* *telithromycin*	*crizotinib* *fingolimod (and metabolite)* *ruxolitinib (and metabolite)*
OATP1B3 (SLCO1B3)	ambrisentan *pralatrexate*	–	*dronedarone (and metabolite)* *telithromycin*	*crizotinib* *fingolimod (and metabolite)* *ruxolitinib (and metabolite)*
OCT (no specific OCT transporter mentioned)	–	linagliptin	–	linagliptin sitagliptin
OCT-1 (SLC22A1)	–	*lenalidomide*	*dronedarone (and metabolite)*	*indacaterol* *ruxolitinib (and metabolite)*
OCT-2 (SLC22A2)	gabapentin varenicline	*pralatrexate* *vandetanib*	dronedarone *ranolazine* *vandetanib*	*indacaterol* *pralatrexate* *ruxolitinib (and metabolite)*
OAT1 (SLC22A6)	–	*lenalidomide* *pralatrexate*	–	*pralatrexate* *ruxolitinib (and metabolite)*
OAT3 (SLC22A8)	sitagliptin *pemetrexed*	*lenalidomide* *pralatrexate*	*dronedarone (and metabolite)*	*pralatrexate* *ruxolitinib (and metabolite)*
MATE1 (SLC47A1)	–	–	–	*indacaterol*
MATE2K (SLC47A2)	–	–	–	*indacaterol*

Italic font indicates that transporter information included in PI was based on data from *in vitro* assessments only.

Regular font plus underline indicates that transporter information included in PI was based on data from *in vivo* DDI studies as indicated in the PIs.

Superscripts a and b indicate that the NMEs are labeled as inducers and non-inducers, respectively, based on *in vitro* or *in vivo* data. NMEs labeled for their transporter induction potential include degarelix (non-P-gp inducer), fingolimod (non-P-gp inducer), indacaterol (non-P-gp and non-MRP2 inducer), saxagliptin (non-P-gp inducer) and tipranavir (P-gp inducer).

Superscript c indicates that although an NME is labeled as an inhibitor, the package insert also includes language indicating that the NME is not expected to be an inhibitor at clinical concentrations (however, no *in vivo* DDI data is available for confirmation).

Superscript d indicates that package insert includes *in vivo* data that lead to a different conclusion as compared to *in vitro* data included in the same package insert. For example, eribulin is labeled as a P-gp substrate and inhibitor *in vitro*, however the package insert also includes data from a DDI study with ketoconazole, labeled as a P-gp/CYP3A4 inhibitor, that did not show increase in C_{max} or AUC of eribulin indicating limited contribution of P-gp in the elimination of eribulin *in vivo*.

The 11 NMEs that were found to be P-gp substrates from *in vitro* assessments and include a ketoconazole DDI study in their PIs without reference to whether this study was conducted to evaluate NME as a P-gp substrate or a CYP3A4 substrate, or both include boceprevir, clobazam, crizotinib, lapatinib, nilotinib, ranolazine, saxagliptin, telaprevir, temsirolimus, ticagrelor, and tolvaptan.

The 17 NMEs whose PIs include digoxin DDI data, without mentioning the involvement of P-gp, are: alfuzosin, darifenacin, eszopiclone, exenatide, gemifloxacin, iloprost, lanthanum, liraglutide, milnacipran, nebivolol, posaconazole, pitavastatin, rosuvastatin, solifenacin, tigecycline, trospium, and vardenafil.

ABC ATP-Binding Cassette; *BCRP* Breast Cancer Resistance Protein; *BSEP* Bile Salt Export Pump; *MATE* Multidrug And Toxic Compound Extrusion; *MCT* Monocarboxylate Transporter; *MRP* Multi-drug Resistance-associated Protein; *NET* Norepinephrine Transporter; *NCTP* Na+-Taurocholate Cotransporting Polypeptide; *OAT* Organic Anion Transporter; *OATP* Organic Anion Transporting Polypeptides; *OCT* Organic Cation Transporter; *P-gp* P-glycoprotein; *SLC* Solute Carrier; *VMAT* Vesicular Monoamine Transporter.

in Table I only if the PI indicated such or included positive *in vivo* data from a DDI study with an inhibitor drug that is specifically referred to as an inhibitor or a substrate for that particular transporter. For example, an NME is listed as an *in vivo* substrate of P-gp when (a) it is shown to be a P-gp substrate *in vitro* and (b) a positive drug interaction is observed in an *in vivo* DDI study conducted with a known P-gp inhibitor drug, such as cyclosporine or ketoconazole (although they may be non-specific for P-gp) where the inhibitor drug was specifically referred to as a 'P-gp inhibitor' in the NME PI (e.g., aliskiren and everolimus). Whereas, if a DDI study was conducted with cyclosporine or ketoconazole but the inhibitor drug was not specifically referred to as a 'P-gp inhibitor' in the NME PI, the NME is not listed as an *in vivo* P-gp substrate in Table I (e.g., boceprevir and ranolazine) even though inhibition with ketoconazole or cyclosporine may partly be due to P-gp in cases where NME is determined to be an *in vitro* P-gp substrate (see Footnotes of Table I for a list of 11 such NMEs). For an NME to be listed as an *in vivo* P-gp inhibitor or non-P-gp inhibitor in Table I, *in vivo* inhibition data with digoxin was considered confirmatory evidence, even if digoxin was not specifically referred to as a P-gp substrate in the PI, because (1) NME PI indicated that NME is a P-gp inhibitor or non-inhibitor *in vitro* and (2) digoxin is a well-established probe substrate for the evaluation of P-gp interactions. Whereas, for NMEs for which a digoxin DDI study was conducted without any reference to whether the NME interacts with P-gp or not in the PIs, the NMEs are not labeled as *in vivo* P-gp inhibitors in Table I, as the *in vivo* DDI study with digoxin could have been conducted for reasons other than to evaluate NME's inhibition effect on P-gp (see Footnotes of Table I for a list of 17 such NMEs). The same general principle is used for classifying NMEs as substrates and/or inhibitors for all other transporters in Table I. It is recommended that readers consider all available DDI information included in the PI of an NME in order to interpret the overall clinical relevance of any transporter-based interactions. The uniform presentation of information in PIs, which may aid in the consistent interpretation of such information, will be addressed in the "Discussion" section of this commentary.

A Comparison of Transporter Information in Package Inserts for NMEs Approved In 2003–2006 vs. 2007–2011

The following observations were made based on our survey of PIs for 88 NMEs approved in 2003–2006 and 95 NMEs approved in 2007–2011.

Inclusion of transporter information (specific transporter names) in NME PIs increased from 24% (21/88) in 2003–2006 to 56% (53/95) in 2007–2011. Information related to P-gp increased from 71% (15/21) in 2003–2006 to 92% (49/53) in 2007–2011. Information related to other transporters such as BCRP, OATPs, OATs, OCTs, etc., increased from 33% (7/21) in 2003–2006 to 38% (20/53) in 2007–2011 (Supplementary Material Table SI).

In addition, 16% (14/88) of NME PIs approved in 2003–2006 and 3% (3/95) of PIs approved in 2007–2011 (Supplementary Material Table SI and Table I, Footnote) included information related to DDI studies with digoxin (a P-gp probe substrate) that may suggest transporter involvement; however, the involvement of specific transporters were not mentioned in the PIs.

Transporter-Related Information in the *Highlights* Section of NME Package Insert

The *Highlights* section in a PI is intended to "provide immediate access to the information that healthcare professionals most commonly refer to and view as most important" under the new Physician Labeling Rule (PLR) format (7). In addition, the "Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products—Content and Format" (8) indicates that, "When clinical pharmacology information has important implications for safe and effective use, it will often appear in other sections of labeling such as *Drug Interactions*, *Warnings and Precautions*, *Dosage and Administration*, or *Contraindications*, and it could appear in the *Highlights of Prescribing Information*." Therefore, as an indicator of the clinical impact and relevance of transporter interactions in the safe and effective use of drugs, we reviewed transporter information included in the *Highlights* section of NME PIs (Table II).

Of the 183 NMEs approved in 2003–2011, 20 NMEs (11%) included transporter-related information in the *Highlights* section of the PIs. Table II contains detailed information on transporter-related interactions including *in vitro* assessments, *in vivo* DDI studies, or both, as indicated in the PIs, that may have been interpreted to support the labeling recommendation in the *Highlights* section, even when specific transporter names were not mentioned.

DISCUSSION

Our analyses suggest that, in concert with recent advances in the area of transporter research, FDA's publication of the 2006 draft DDI Guidance, along with other concurrent scientific discussions, may have encouraged drug development companies to more comprehensively evaluate the role of transporters in the ADME of a drug and incorporate transporter-related information in new drug applications (NDAs), as indicated by the increased amount of transporter information in NME PIs approved in 2007–2011 compared to 2003–2006. We observed that *in vivo* DDI studies with

Table II Transporter Information in the *Highlights* Section of Package Inserts of New Molecular Entities (Approved 2003–2011)

Year of approval	Drug names; Generic and (BRAND)	Transporter related information in the *Highlights* section	Approval date of the latest PI as of March 29, 2012	Implicated transporters[a]	Supporting data as indicated in PI	Comments
2003	Rosuvastatin (CRESTOR)	Cyclosporine: Combination increases rosuvastatin exposure. Limit CRESTOR dose to 5 mg once daily. (2.5,7.1)	02/28/2012	*OATP1B1 and BCRP* (ref. 11)	Section 12.3: DDI study of rosuvastatin (10 mg QD for 10 days) with cyclosporine (75–200 mg BID) : Change in AUC of rosuvastatin: 7 fold Change in Cmax of rosuvastatin: 11 fold	No particular transporter is indicated to be involved in the DDI of rosuvastatin with cyclosporine in rosuvastatin's PI. However, from literature (ref. 11) and PI for PROMACTA, rosuvastatin is an OATP1B1 and BCRP substrate. Cyclosporine is known to inhibit OATP1B1 and BCRP (refs 12, 13).
2004	Pemetrexed (ALIMTA)	Nephrotoxic drugs: Concomitant use of these drugs and/or substances which are tubularly secreted may result in delayed dearance. (7.2)	11/18/2011	OAT3	Section 7.2: "Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of ALIMTA"	PI indicates that pemetrexed is an *in vitro* substrate for OAT3 (Section 12.3).
2005	Conivaptan (VAPRISOL)	Exposure to coadministered digoxin may be increased and digoxin levels should be monitored (5.4, 7.2).	02/01/2012	P-gp	Section 5.4, 7.2: DDI study of conivaptan (40 mg BID) and digoxin (0.5 mg): Change in AUC of digoxin: 1.4 fold; Change in Cmax of digoxin: 1.8 fold; Change in clearance of digoxin: ↓ 30%	PI indicates that P-gp may be involved in the conivaptan-digoxin interaction (Section 7.2).
2006	Posaconazole (NOXAFIL)	Digoxin: Monitor digoxin plasma concentrations (7.12)	9/8/2010	*P-gp*	Section 7.12: "Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole"	Interaction between posaconazole and digoxin may be due to P-gp. However, inhibition effect of posaconazole on P-gp is not mentioned in the PI or available in the literature. Posaconazole is a strong inhibitor for CYP3A. *In vivo* inhibition on drugs that are dual CYP3A and P-gp substrates (e.g., sirolimus, simvastatin) (posaconazole PI, Drugs@FDA) may be partly due to P-gp inhibition.
2006	Ranolazine (RANEXA)	P-gp inhibitors (e.g., cyclosporine): May need to lower Ranexa dose based on clinical response. (7.1)	12/21/2011	P-gp	Section 7.1: "Concomitant use of Ranexa and P-gp inhibitors, such as cyclosporine, may result in increases in ranolazine concentrations." Section 12: DDI study of ranolazine (1000 mg BID) with ketoconazole (200 mg BID): Change in "plasma levels" of ranolazine: 3.2 fold.	PI indicates that ranolazine is a P-gp substrate and inhibitor (Section 12.3).
		Drugs transported by P-gp or metabolized by CYP2D6 (e.g., digoxin, tricyclic antidepressants): May need reduced doses of these drugs when used with Ranexa. (7.2)		P-gp	Section 12.3 : DDI study of ranolazine (1000 mg BID) with digoxin (0.125 mg) : Change in digoxin concentration: 1.5 fold	
2006	Darunavir (PREZISTA)	Co-administration of PREZISTA/ritonavir with other drugs can alter the concentration of other	02/17/2012	P-gp	Section 12.3 : DDI study of darunavir/ritonavir (600/100mg BID) with digoxin (0.4 mg):	PI indicates that darunavir is a P-gp inhibitor (Section 12.3).

Table II (continued)

Year of approval	Drug names; Generic and (BRAND)	Transporter related information in the *Highlights* section	Approval date of the latest PI as of March 29, 2012	Implicated transporters[a]	Supporting data as indicated in PI	Comments
		drugs and other drugs may alter the concentrations of darunavir. The potential drug-drug concentrations must be considered prior to and during therapy. (4, 5.5, 7, 12.3).			Change in Cmax and AUC of digoxin: 1.15 fold and 1.36 fold respectively.	
2007	Ambrisentan (LETAIRIS)	Multiple dose co-administration of ambrisentan and cyclosporine resulted in an about 2-fold increase in ambrisentan exposure in healthy volunteers. When co-administered with cyclosporine, limit the dose to 5 mg once daily (7).	02/15/2012	P-gp, OATP1B1, OATP1B3	Section 7: "Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers" Section 12.3: DDI study with cyclosporine: Change in Cmax and AUC of aliskiren: ~1.5 fold and ~2.25 fold, respectively.	PI indicates that ambrisentan is a P-gp, OATP1B1 and OATP1B3 substrate (Section 12.3).
2007	Lapatinib (TYKERB)	TYKERB is likely to increase exposure to concomitantly administered drugs which are substrates of CYP3A4, CYP2C8, or P-glycoprotein (ABCB1). (7.1)	02/14/2012	P-gp	Section 7.1: DDI study with digoxin: Change in AUC of digoxin: 2.8 fold.	PI indicates that lapatinib is a P-gp inhibitor (Section 7.1).
2007	Aliskiren (TEKTURNA)	Cyclosporine: Avoid concomitant use (7, 12.3) Itraconazole: Avoid concomitant use (7, 12.3)	02/02/2012	P-gp and *OATP2B1* (ref 14)	Section 12.3: DDI study with cyclosporine (600 mg): Change in Cmax and AUC of aliskiren: ~3 fold and ~5 fold respectively (Figure 1 in PI); DDI study with itraconazole (100 mg BID): Change in Cmax and AUC of aliskiren: ~5 fold and ~6 fold, respectively (Figure 1 in PI).	PI indicates that P-gp is involved in absorption and disposition of aliskiren (Section 12.3). Literature indicates that aliskiren may be an OATP2B1 substrate (ref 14).
2008	Eltrombopag (PROMACTA)	Eltrombopag is an inhibitor of OATP1B1 and BCRP transporters. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP (e.g., rosuvastatin) and consider reduction of the dose of these drugs. (7.2)	12/6/2011	OATP1B1 and BCRP	Section 7.2: DDI study of eltrombopag (75 mg once daily for 5 days) with rosuvastatin (single 10 mg dose) indicated as an OATP1B1 and BCRP substrate: Change in Cmax and AUC of eltrombopag: 2 fold and 1.55 fold, respectively.	PI indicates that eltrombopag is a BCRP and OATP1B1 inhibitor (*Highlights*, Section 7.2).
2008	Silodosin (RAPAFLO)	Strong P-glycoprotein inhibitors (e.g., cyclosporine): Coadministration may increase plasma silodosin concentration. Concomitant use is not recommended. (7.2)	3/4/2010	P-gp	Section 7.1: DDI study with ketoconazole (400 mg): Change in Cmax and AUC of silodosin: 3.8 fold and 3.2 fold, respectively. Section 12.3: "A drug interaction study with a strong P-gp inhibitor has not been conducted."	PI indicates that silodosin is a P-gp substrate (Sections 7.2 & 12.3).
2008	Etravirine (INTELENCE)	Co-administration of INTELENCE® with drugs that are	03/26/2012	P-gp	Section 12.3: DDI study with digoxin (0.5 mg): Change in Cmax and AUC of	PI indicates that etravirine is a P-gp inhibitor (Sections 7 & 12.3). However, a change in digoxin dosing

Table II (continued)

Year of approval	Drug names; Generic and (BRAND)	Transporter related information in the *Highlights* section	Approval date of the latest PI as of March 29, 2012	Implicated transporters[a]	Supporting data as indicated in PI	Comments
		substrates of CYP3A, CYP2C9, and/or CYP2C19 or are transported by P-glycoprotein may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s) (7).			digoxin: 1.19 fold and 1.18 fold, respectively.	regimen is not recommended indicating that P-gp inhibition by etravirine is probably not considered clinically significant.
2009	Dronedarone (MULTAQ)	Digoxin: Consider discontinuation or halve dose of digoxin before treatment and monitor (7.1, 7.3).	01/25/2012	P-gp	Section 12.3: DDI study with digoxin: Change in Cmax and AUC of digoxin: ~2 and ~2.5 fold, respectively (Figure 2 in PI)	PI indicates that dronedarone is a P-gp (*Highlights*, Sections 7.3 & 12.3), OATP1B1 and OATP1B3 inhibitor (Section 12.3).
		Statins: Avoid simvastatin doses greater than 10 mg daily. Follow label recommendations for concomitant use of other statins with a CYP 3A and P-gp inhibitor like dronedarone (7.3)		P-gp, OATP1B1 and OATP1B3	Section 12.3: DDI study with simvastatin: Change in Cmax and AUC of simvastatin: ~4 fold (Figure 2 in PI).	
2009	Tolvaptan (SAMSCA)	Consider dose reduction if co-administered with P-gp inhibitors (5.5)	02/01/2012	P-gp	Section 5.5: "The dose of SAMSCA may have to be reduced when SAMSCA is co-administered with P-gp inhibitors, e.g., cyclosporine."	PI indicates that tolvaptan is a P-gp substrate (Sections 2.3 & 12.3) and inhibitor (Section 7.2 & 12.3). A DDI study with a specific P-gp inhibitor was not performed. A DDI study with digoxin was performed.
2009	Everolimus (AFINITOR)	If moderate inhibitors of CYP3A4 and/or P-glycoprotein (PgP) are required, reduce the AFINITOR dose to 2.5 mg once daily; if tolerated, consider increasing to 5 mg once daily. (2.2)	5/5/2011	P-gp	Section 7.1: DDI study with ketoconazole: Change in Cmax and AUC of everolimus: 3.9 fold and 15 fold, respectively; DDI study with erythromycin: Change in Cmax and AUC of everolimus: 2.0 fold and 4.4 fold, respectively;	PI indicates that everolimus is a substrate and inhibitor of P-gp (Sections 7 and 12.3). A DDI study with a P-gp substrate was not performed.
		Moderate CYP3A4 and/or PgP inhibitors: If combination is required, use caution and reduce dose of AFINITOR. (2.2, 2.4, 5.6, 7.1)			DDI study with verapamil: Change in Cmax and AUC of everolimus: 2.3 fold and 3.5 fold, respectively.	
2010	Dabigatran (PRADAXA)	P-gp inducers rifampin: Avoid coadministration with PRADAXA (5.3)	01/17/2012	P-gp	Section 12.3: DDI study with rifampin (600 mg once daily for 7 days): Change in Cmax and AUC of dabigatran: ↓ 67% and ↓ 66%, respectively. By Day 7 after cessation of rifampin treatment, dabigatran exposure was close to normal.	PI indicates dabigatran etexilate is a P-gp substrate (Section 12.3).
		P-gp inhibitors dronedarone and systemic ketoconazole in patients with moderate renal impairment (CrCl 30-50 mL/min): Consider reducing PRADAXA dose to 75 mg twice daily (7)		P-gp	Section 12.3: "Exposure to dabigatran is higher when it is administered with dronedarone than when it is administered alone (73–99%)." DDI study with single-dose ketoconazole: Change in Cmax and AUC of dabigatran: ~2.4 fold for both. DDI study with multiple-dose ketoconazole:	

Table II (continued)

Year of approval	Drug names; Generic and (BRAND)	Transporter related information in the *Highlights* section	Approval date of the latest PI as of March 29, 2012	Implicated transporters[a]	Supporting data as indicated in PI	Comments
		P-gp inhibitors in patients with severe renal impairment (CrCl <30 mL/min): PRADAXA use not recommended (7)			Change in Cmax and AUC of dabigatran: ~2.5 fold for both.	
2011	Linagliptin (TRADJENTA)	P-glycoprotein/CYP 3A4 inducer: The efficacy of TRADJENTA may be reduced when administered in combination (e.g., with rifampin). Use of alternative treatments is strongly recommended. (7.1)	5/2/2011	P-gp	Section 7.1: "Rifampin decreased linagliptin exposure…" Section 12.3: DDI study of rifampin (600 mg QD) with linagliptin (5 mg QD): Change in geometric mean ratios of Cmax and AUC of linagliptin: 0.56 and 0.6, respectively.	PI indicates that linagliptin is a P-gp substrate (Section 12.3).
2011	Ezogabine (POTIGA)	N-acetyl metabolite of ezogabine may inhibit renal clearance of digoxin, a P-glycoprotein substrate. Monitor digoxin levels. (7.2)	03/19/2012	P-gp	Section 7.2: "Data from an *in vitro* study showed that the N-acetyl metabolite of ezogabine (NAMR) inhibited P-glycoprotein–mediated transport of digoxin in a concentration-dependent manner, indicating that NAMR may inhibit renal clearance of digoxin."	PI indicates that N-acetyl metabolite of ezogabine is a P-gp inhibitor (Sections 7.2 & 12.3). A DDI study with digoxin was required as a post-marketing requirement study.
2011	Rivaroxaban (XARELTO)	Combined P-gp and strong CYP3A4 inhibitors: Avoid concomitant use unless the lack of a significant interaction is proven (7.1)	7/1/2011	P-gp	Section 7.1: DDI study with ketoconazole: Change in Cmax and AUC of rivaroxaban: 1.7 fold and 2.6 fold, respectively. DDI study with ritonavir: Change in Cmax and AUC of rivaroxaban: 1.6 fold and 2.5 fold, respectively. DDI study with clarithromycin: Change in Cmax and AUC of rivaroxaban: 1.4 fold and 1.5 fold, respectively. DDI study with erythromycin: Change in Cmax and AUC of rivaroxaban: 1.3 fold for both.	PI indicates that rivaroxaban is a P-gp substrate (Sections 7 & 12.3).
		Combined P-gp and weak or moderate CYP3A4 inhibitors: Avoid concomitant use Unless the benefit outweighs the bleeding risk in patients with renal impairment (7.2)		P-gp	Section 7.2: "Based on simulated pharmacokinetic data, patients with renal impairment receiving XARELTO with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected."	
		Combined P-gp and strong CYP3A4 inducers: Avoid concomitant use		P-gp	Section 7.3: DDI study of rivaroxaban (20 mg single dose with food) with	

Table II (continued)

Year of approval	Drug names; Generic and (BRAND)	Transporter related information in the *Highlights* section	Approval date of the latest PI as of March 29, 2012	Implicated transporters[a]	Supporting data as indicated in PI	Comments
		or consider an increased dose (2.1, 7.3)			rifampicin (titrated up to 600 mg once daily): Change in Cmax and AUC of rivaroxaban: ↓ 22% and ↓ 50%, respectively.	
2011	Ticagrelor (BRILINTA)	Monitor digoxin levels with initiation of or any change in BRILINTA. (7.4)	7/20/2011	P-gp	Section 12.3: DDI study of ticagrelor (400 mg QD) with digoxin (0.25 mg): Change in Cmax and AUC of digoxin: ~1.75 fold and ~1.25 fold, respectively.	PI indicates that ticagrelor and its active major metabolite are substrates and inhibitors of P-gp (Sections 12.3).

Source: Drugs@FDA

[a] *Italic font* indicates possible transporter involvement (no specific transporter is mentioned in PI).

digoxin were conducted more frequently without prior *in vitro* assessments in 2003–2006 period (16%, 14/88) compared to the 2007–2011 period (3%, 3/95). This finding suggests that the P-gp decision tree proposed by the FDA in the 2006 draft DDI Guidance and subsequent publications may have informed the decision-making process to evaluate the necessity of an *in vivo* digoxin DDI study during drug development (1,9,10). It should be noted that in our analyses, we examined the most recently updated PIs; therefore, transporter information included in the PIs may have been added post-approval and our findings may not necessarily portray transporter information included in the PI at the time of NDA approval.

P-gp appears to be the most widely studied transporter in NME drug development. Transporters other than P-gp, such as BCRP, OATPs, OATs, OCTs, etc., have been more recently included in NME PIs, indicating that interactions involving transporters other than P-gp are being increasingly recognized and studied during drug development. These transporters are also among the primary transporters recommended for study during drug development by the ITC (1, 2), EMA (5) and FDA (3, 4).

Inclusion of transporter-related information in the 'Highlights' section of the PI suggests that over the past decade, transporter-based interactions have been recognized as clinically relevant. During our analyses, four major types of dosing recommendations based on transporter interactions were noted in the *Highlights* section:

a. Avoid use of the NME with a concomitantly administered drug or suggest use of alternate therapies. Examples include PIs for aliskiren, silodosin, dabigatran, linagliptin and rivaroxaban (all based on P-gp interactions).
b. Reduce dose of the NME or a concomitantly administered drug by a specific amount. Examples include PIs for ambrisentan (a P-gp substrate), dronedarone (a P-gp inhibitor) and everolimus (a P-gp substrate).
c. Consider a dose reduction of the NME or a concomitantly administered drug with no specific dosing recommendation. Examples include PIs for eltrombopag (an OATP1B1 and BCRP inhibitor), ranolazine (a P-gp substrate) and tolvaptan (a P-gp substrate).
d. Monitor digoxin levels. Examples include PIs for conivaptan, darunavir, lapatinib, etravirine, ezogabine and ticagrelor (based on P-gp inhibition).

Labeling is an important communication tool for health care practitioners to understand risk-benefit profile of a drug. Managing DDI is an important component for minimizing adverse events related to polypharmacy. In the 2012 FDA's revised draft DDI Guidance (4), the following general principles regarding DDI labeling are stated:

a. In general, include clinically relevant actionable instructions in the Drug Interactions section (Section 7). The

supporting pharmacokinetic data including *in vivo* or *in vitro* data should be included in the Clinical Pharmacology section (Section 12).

b. When drug interaction information has important implications for the safe and effective use of the drug, the information may be distributed among several other PIs sections (e.g., Highlights, Dosage and Administration, Contraindications, Warnings and Precautions, or Patient Counseling Information), with a cross-reference to the Drug Interactions or Clinical Pharmacology section for more detailed information.

In general, labeling pertaining to transporter-related DDI should follow these guidelines. Because the study of drug transporters continues to evolve, and in order to ensure consistency in labeling and to assist health care practitioners and patients in their understanding of the mechanistic and clinical implications of transporter-mediated drug interactions, we provide the following considerations for labeling based on language included in some NME PIs that we believe communicate transporter-related information in an effective way:

- Include *in vitro* transporter data in the PIs and indicate whether an NME has a potential for clinical interactions as either a transporter substrate or an inhibitor when a clinical follow-up study was not conducted. This information may be helpful in instilling caution when a DDI is suspected based on *in vitro* data, and when confirmatory *in vivo* DDI data are not available at the time of approval of the NDA.
- Include a brief explanation in the PI when *in vitro* and *in vivo* DDI data are not in obvious agreement with each other. For example, if an NME is labeled as a P-gp inhibitor based on an *in vitro* assessment, but data from an *in vivo* digoxin DDI study shows an insignificant interaction, the PI should include an explanation acknowledging this difference between *in vitro* and *in vivo* data to guide healthcare practitioners in understanding the overall clinical implication. In particular, when this information is split in two sections, such as Sections 7 and 12, it is important that the information is referenced to each other so that the overall *in vivo* DDI implication is clear.
- Include the specific transporter name for which a drug is employed as a substrate or an inhibitor in an *in vivo* DDI study in the PI whenever possible. If the mechanism of a drug interaction is known to be mediated by a particular transporter, the transporter should be mentioned in the PI to indicate the scientific rationale for conducting that DDI study. In doing so, healthcare practitioners may be able to extrapolate the DDI information to other drugs that may have similar interaction mechanisms. As an example, when an NME is found to be both a P-gp and CYP3A4 substrate based on *in vitro* assessments, and an *in vivo* DDI study is conducted with ketoconazole, the PI should refer to ketoconazole as both a P-gp and a CYP3A4 inhibitor because positive *in vivo* DDI data with ketoconazole indicate possible P-gp and CYP3A4 involvement in NME disposition and negative *in vivo* data will exclude both. If the PI only referred to ketoconazole as a CYP3A4 inhibitor, the information on the P-gp involvement of NME disposition may be missed, i.e. the potential for NME interaction with other P-gp inhibitors may be missed. Similarly, if the goal of an *in vivo* DDI study with digoxin (a probe P-gp substrate) is to confirm the *in vivo* P-gp inhibitory potential of an NME, it is helpful to refer to digoxin as a P-gp substrate in the PI. Negative *in vivo* data with digoxin will exclude NME's effect on P-gp. Positive *in vivo* data can implicate NME's *in vivo* effect on P-gp, although it may not be exclusively attributed to P-gp. Therefore, appropriate description of transporter information in the PI is helpful to interpret the overall clinical relevance of transporter-based interactions.
- Include negative results from both *in vitro* transporter assessments and *in vivo* DDI studies, if available, in the PIs. If negative data is excluded from the PIs, it may be viewed as "unknown". Negative results may guide drug usage in a clinically relevant manner, especially for drugs that may not exhibit the same transporter interaction potential as other drugs in its class or in therapeutic areas such as oncology, where multiple drugs are frequently co-administered.
- Include succinct and clinically actionable information in the *Highlights* section of the PI. The PK or PD interaction data or expected interaction may be described in further detail in other sections of the PI, such as *Drug Interactions* or *Clinical Pharmacology*.

CONCLUSION

Since the publication of the FDA's draft DDI Guidance in 2006 recommending the inclusion of transporter-based interactions as a part of the overall DDI evaluation of a new molecular entity (NME), transporter interactions are being studied to various degrees during drug development as indicated by the abundance of transporter information in the package inserts (PIs) of recently approved NMEs based on our analyses. With the publication of the new 2012 FDA's revised draft DDI Guidance, we expect that transporter-related evaluations of NMEs will be streamlined to focus on the most clinically relevant transporters, with the ultimate goal of presenting clinically actionable information in the PI that may be easily located and interpreted by health care practitioners and patients.

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