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Title

What Can Be Learned from Recent New Drug Applications? A Systematic Review of Drug Interaction Data for Drugs Approved by the U.S. FDA in 2015

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Running Title Page

a) Running title: A review of drug disposition and DDIs in 2015 NDAs

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d) Abbreviations:

AhR, aryl hydrocarbon receptor; AO, aldehyde oxidase; AUC, area under the time-plasma concentration curve; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CrCL, creatinine clearance; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; DIDB, University of Washington Drug Interaction Database®; DME, drug metabolizing enzyme; EM, extensive metabolizer; EMA, European Medicines Agency; FDA, Food and Drug Administration; FMO, flavin-containing monooxygenase; HI, hepatic impairment; HLM, human liver microsomes; PXR, human pregnane X receptor; IM, intermediate metabolizer; MATE, multidrug and toxin extrusion; MRP, multidrug resistance-associated protein; NTI, narrow therapeutic index; NDA, new drug application; NME, new molecular entity; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P450, cytochrome P450; PBPK, physiologically-based pharmacokinetics, PGx, pharmacogenetics(s); P-gp, P-glycoprotein; PK, pharmacokinetic(s); PM, poor metabolizer; PMR, post-

marketing requirement; RI, renal impairment; SULT, sulfotransferase; TDI, time-dependent inhibition; UGT, UDP-glucuronosyltransferase; URAT1, urate anion exchanger 1

Abstract

As a follow-up to previous reviews, the aim of the present analysis was to systematically examine all drug metabolism, transport, PK, and DDI data available in the 33 NDAs approved by the FDA in 2015, using the University of Washington Drug Interaction Database©, and to highlight the significant findings. In vitro, a majority of the NMEs were found to be substrates or inhibitors/inducers of at least one DME or transporter. In vivo, 95 clinical DDI studies displayed positive PK interactions, with an AUC ratio ≥ 1.25 for inhibition or ≤ 0.8 for induction. When NMEs were considered as victim drugs, 21 NMEs had at least one positive clinical DDI, with three NMEs shown to be sensitive substrates of CYP3A (AUC ratio ≥ 5 when coadministered with strong inhibitors): cobimetinib, isavuconazole (the active metabolite of prodrug isavuconazonium sulfate), and ivabradine. As perpetrators, nine NMEs showed positive inhibition and three NMEs showed positive induction, some of these interactions involving both enzymes and transporters. The most significant changes for inhibition and induction were observed with rolapitant, a moderate inhibitor of CYP2D6 and lumacaftor, a strong inducer of CYP3A. PBPK simulations and PGx studies were used for six and eight NMEs, respectively, to inform dosing recommendations. The effects of hepatic or renal impairment on the drugs' PK were also evaluated to support drug administration in these specific populations.

Introduction

Understanding the risk of pharmacokinetic (PK)-based drug-drug interactions (DDIs) with newly marketed drugs is critical to allow the safe utilization of new molecular entities (NMEs) in clinical practice. In recent years, the use of in vitro-in vivo extrapolation models for DDI risk assessment has improved how we can predict and prevent DDIs, utilizing data from human in vitro systems and the well-standardized and mechanistic framework for in vivo evaluations. In two previous publications (Yu et al., 2014; Yu et al., 2016), we described the results of extensive in vitro and clinical evaluations of recent NMEs (approved by the FDA in 2013 and 2014) using probe substrates and inhibitors/inducers of drug metabolizing enzymes and transporters, and how this information was used to support product labeling recommendations. As a follow-up, the present review includes a detailed analysis of the pre-clinical and clinical enzyme- and transporter-mediated DDIs observed for NDAs approved by the FDA in 2015, highlighting the main mechanistic findings and discussing their clinical relevance. The analysis was performed using the University of Washington Drug Interaction Database© (DIDB) drug interactions, pharmacogenetics (PGx), and organ impairment modules (http://www.druginteractioninfo.org) and follows the same methodology as previously described (Yu et al., 2014; Yu et al., 2016).

A total of 33 NDAs were approved by the FDA and are summarized in Table 1, with the chemical structures presented in Supplemental Table 1. The most represented therapeutic areas were oncology drugs (30%), followed by cardiovascular drugs, central nervous system agents, and anti-infective agents, with four drugs approved (12%) in each class. All of the NDAs had drug metabolism and/or transporter data available and therefore are fully analyzed in this review. Among them, 22 (67%) were evaluated in patients with various degrees of organ impairment, eight (24%) presented PGx information, and seven (21%) had PBPK simulation data. Of note, six NMEs were administered as prodrugs, namely aripiprazole lauroxil, isavuconazonium sulfate, ixazomib citrate, sacubitril, tenofovir alafenamide sulfate, and uridine triacetate, with their respective metabolites aripirazole, isavucoanzole, ixazomib, LBQ657, tenofovir, and uridine being pharmacologically active. However, only three of the active metabolites are newly approved

chemical entities - isavuconazole, ixazomib, and sacubitril metabolite LBQ657, and are presented in this review. Finally, five NDAs described combination drugs: ACYCAZ (ceftazidime and avibactam), ENTRESTO (sacubitril and valsartan), GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate), LONSURF (trifluridine and tipiracil), and ORKAMBI (lumacaftor and ivacaftor), in which only avibactam, lumacaftor, savubitril, tenofovir alafenamide fumatrate, and tipiracil are NMEs and discussed in this review.

Metabolism and Enzyme-Mediated DDIs

Thirty NMEs approved in 2015 were evaluated in vitro as substrates, inhibitors, and/or inducers of clinically important drug metabolizing enzymes (DMEs). When considered as substrates, 27 NMEs were shown to be metabolized by at least one enzyme, with the majority primarily metabolized by one or more P450 (Table 2 and Figure 1A). As expected, and similarly to approvals from the previous two years (Yu et al., 2014; Yu et al., 2016), CYP3A4/5 was shown to metabolize the largest number of NMEs in vitro, although not necessarily as the major enzyme. In vivo studies further confirmed that 12 of these NMEs were indeed clinical CYP3A substrates, with systemic exposure increases ≥ 25% when coadministered with the strong CYP3A inhibitors itraconazole (200 mg orally once daily), ketoconazole (200 orally once or twice daily or 400 mg orally once daily), or posaconazole (400 mg orally twice daily), resulting in the following maximum AUC and C_{max} ratios (in decreasing order of magnitude): ivabradine, 7.70 and 3.60; cobimetinib, 6.70 and 3.20; isavuconazole (the active metabolite of prodrug isavuconazonium sulfate), 5.22 and 1.09; flibanserin, 4.61 and 1.84; cariprazine, 3.78 and 3.26; daclatasvir, 3.00 and 1.57; sonidegib, 2.26 and 1.50; brexpiprazole, 2.17 and 1.18; palbociclib, 1.85 and 1.35; alectinib, 1.75 and 1.18; panobinostat, 1.70 and 1.60; and trabectedin, 1.66 and 1.22, respectively. Of note, six of these NMEs are also substrates of P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) (Table 2), and inhibition of those transporters may also contribute to the observed increased exposure (details of which are reviewed in the following transporter section). Based on the FDA classification, ivabradine, cobimetinib, and isavuconazole can be considered sensitive substrates of CYP3A, with AUC ratios ≥ 5 in

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the presence of strong CYP3A inhibitors, the significant changes in exposure suggesting a primary role of CYP3A in the disposition of these drugs ($f_{m,\ CYP3A} \geq 0.8$). Based on these results, concomitant use of strong CYP3A inhibitors with ivabradine (FDA, 2015f) and isavuconazonium sulfate (FDA, 2015g) is contraindicated, and should be avoided with cobimetinib (FDA, 2015z). Coadministration of the moderate CYP3A inhibitors diltiazem (120 mg orally twice daily), verapamil (120 mg orally twice daily), and grapefruit juice (dosing regimen unavailable) resulted in a 2- to 3-fold increase in ivabradine AUC and C_{max}, and a 20-60% increase in its active metabolite, S18982, exposure. On the basis of these results, concomitant use of moderate CYP3A inhibitors with ivabradine should be avoided (FDA, 2015f). For cobimetinib, the interactions with less potent CYP3A inhibitors were studied using PBPK simulations. It was predicted that moderate CYP3A inhibitors diltiazem (1200 mg orally twice daily) and erythromycin (500 mg orally three times daily) could increase cobimetinib AUC by 3.3- to 4.3-fold and C_{max} by 1.9- to 3.8-fold, respectively, whereas coadministration of fluvoxamine (100 mg orally once daily), a known weak inhibitor of CYP3A, would not affect the exposure of cobimetinib to any significant extent. According to the product label, concomitant use of moderate CYP3A inhibitors with cobimetinib should be avoided. If avoiding concurrent use is not possible, a dose reduction of cobimetinib could be considered (FDA, 2015z). For isavuconazonium sulfate, coadministration of lopinavir/ritonavir (400 mg/100 mg orally twice daily), both CYP3A strong inhibitors, increased the exposure to isavuconazole by approximately 2-fold, and caution is recommended when isavuconazonium sulfate is coadministered with lopinavir/ritonavir with monitoring for the signs of isavuconazole toxicity (FDA, 2015g). For the remaining nine drugs with $1.25 \leq$ AUC ratios < 5 in the presence of a strong CYP3A inhibitor, concomitant use with strong CYP3A inhibitors is either contraindicated (flibanserin), to be avoided (palbociclib, sonidegib, and trabectedin), or dose reduction should be considered (brexpiprazole (FDA, 2015p), cariprazine (FDA, 2015v), daclatasvir (FDA, 2015h), and panobinostat (FDA, 2015j), according to the drugs' respective product labels; however, no dose adjustment is recommended for patients taking strong CYP3A inhibitors with alectinib, as the effect of posaconazole on alectinib exposure (AUC ratio = 1.75) was not considered clinically meaningful by the sponsor (FDA, 2015b). As expected, most of these

drugs (except cariprazine, which was not evaluated with strong inducers) were also sensitive to induction by rifampin (600 mg orally once daily) or St. John's Wort extract (300 mg orally three times daily), yielding labeling recommendations for all of them (with the exception of alectinib) when coadministered with strong inducers of CYP3A.

Based on pre-clinical studies, other P450 isoforms, namely CYP2D6, CYP2C8, CYP2C19, CYP2C9, and CYP2B6, were also involved in the metabolism of six, four, four, three, and two NMEs, respectively (Figure 1A). However, contributions from these enzymes to the drugs' overall disposition were considered limited, and no drugs were identified as sensitive substrates of any of these enzymes based on the follow-up clinical studies. The highest AUC change was observed with brexpiprazole, with a 2-fold increase in CYP2D6 extensive metabolizers (EMs) when coadministered with quinidine (324 mg orally once daily), a strong CYP2D6 inhibitor. Similarly, brexpiprazole AUC increased to the same level after coadministration of ketoconazole (200 mg orally twice daily), a strong CYP3A inhibitor, indicating possible equal contribution of both CYP3A and CYP2D6 to the drug's metabolism. Additionally, several NMEs were found to be primarily metabolized by non-P450 enzymes: edoxaban and selexipag, which are mainly metabolized by hepatic carboxyesterase 1 (CES1) with minor contributions from P450s; aripiprazole lauroxil, isavuconazonium sulfate, sacubitril, and uridine triacetate, as prodrugs, which are rapidly hydrolyzed in blood by esterases to their active metabolites, with P450s involved in the subsequent metabolism of some of the active metabolites; tenofovir alafenamide fumarate, which is metabolized to its major active metabolite tenofovir by cathepsin A in peripheral blood monocellular cells and by CES1 in hepatocytes; cangrelor, which is metabolized by nucleotidases in plasma; and finally, lenvatinib, which is mainly metabolized by aldehyde oxidase, in addition to minor contributions from CYP3A4 and other P450 enzymes.

When NMEs were considered as perpetrators, 29 were investigated in vitro for the potential to inhibit DMEs. Twenty-one NMEs inhibited at least one P450 enzyme or UDP-glucuronosyltransferase (UGT) (Table 3), with the most affected enzymes being CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6,

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CYP2B6, and UGT1A1 (Figure 1B). In addition, 12 major metabolites of 10 NMEs (including four metabolites of prodrugs) were also found to inhibit specific P450 enzymes (Table 3). With regard to the mechanism of inhibition, 10 NMEs and three metabolites were evaluated for TDI of P450 enzymes, and a majority, comprising 8 NMEs and 2 metabolites, showed TDI of one or more P450 enzyme, in particular, CYP3A4/5. Alectinib and palbocilicib, both the parent drugs and the metabolites (alectinib metabolite M4 and palbociclib metabolite M17) were time-dependent inhibitors of CYP3A4/5.

Based on the R_1 and R_2 values (FDA, 2012), the majority of the in vitro inhibitory interactions were not considered clinically relevant (R_1 or $R_2 \leq 1.1$). Among drugs with R_1 or $R_2 > 1.1$ (n = 11), in vivo studies and PBPK simulations with P450 probe substrates found only four NMEs with positive enzyme inhibition: isavuconazole (dosing regimen unavailable) and rolapitant (200 mg single dose) were found to moderately inhibit probe substrates of CYP3A (midazolam AUC ratio = 2.03, C_{max} ratio = 1.72) and CYP2D6 (dextromethorphan AUC ratio = 3.33, C_{max} ratio = 2.77), respectively; panobinostat (200 mg orally once daily) was a weak-to-moderate inhibitor of CYP2D6 (dextromethorphan AUC ratio = 1.20-2.30, C_{max} ratio = 1.20-2.30); flibanserin (50 mg orally twice daily) was a weak inhibitor of CYP3A (simvastatin AUC ratio = 1.31, C_{max} ratio = 1.15; simvastatin acid AUC ratio = 1.47, C_{max} ratio = 1.36), and rolapitant (200 mg single dose) was a weak inhibitor of CYP2B6 (efavirenz AUC ratio = 1.32, C_{max} ratio = 1.09) and CYP2C19 (omeprazole AUC ratio = 1.34, C_{max} ratio = 1.48). The moderate (isavuconazole and rolapitant) and weak-to-moderate (panobinostat) inhibition interactions were all reflected in the respective labels (FDA, 2015g; FDA, 2015s; FDA, 2015j). As expected, the majority of drugs with R values below the cut-off of 1.1 were not evaluated clinically. However, those that were assessed in a clinical study actually showed weak inhibition of P450 enzymes: lesinurad (400 mg single dose; repaglinide AUC ratio = 1.31, C_{max} ratio = 1.27) and rolapitant (200 mg single dose; repaglinide AUC ratio = 1.27, C_{max} ratio = 1.26) showed weak inhibition of CYP2C8; and palbociclib (125 mg once daily) showed weak inhibition of CYP3A (midazolam AUC ratio = 1.58, C_{max} ratio = 1.38). The effects of lesinurad and rolapitant were not considered clinically significant and no dose adjustment is needed,

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whereas the label for palbociclib specifies that "the dose of sensitive CYP3A substrates with a narrow therapeutic index (NTI) may need to be reduced as concurrent administration of palbociclib may increase their exposure" (FDA, 2015k). Of note, two drugs with R_1 values > 1.1, namely sonidegib and osimertinib, had not been evaluated clinically at the time of their approval. Sonidegib was a potent inhibitor of CYP2B6 (K_i = 0.045 μM, R_1 = 34) and CYP2C9 (K_i = 1.7 μM, R_1 = 1.8) in vitro, and clinical studies to evaluate the effect of sonidegib on these two enzymes are currently being performed by the sponsor. For osimertinib, which showed in vitro inhibition of CYP3A (IC_{50} = 5.1 μM, R_1 > 1.1), a clinical study to evaluate the effect of repeated dosing of osimertinib on the PK of a CYP3A probe substrate was requested as a post-marketing requirement (PMR). On the basis of the in vitro study results, concomitant administration of osimertinib with sensitive substrates of CYP3A should be avoided (FDA, 2015ae).

When evaluating the in vitro findings by enzyme, the largest number of NMEs (15 drugs and seven metabolites, including two active metabolites from prodrugs) showed inhibition of CYP3A4/5 (Figure 1B); however, only three NMEs showed positive inhibition of CYP3A clinically as discussed above. A significant number of NMEs (eight drugs and two active metabolites including one from a prodrug) showed some inhibition of CYP2C8 in vitro (Figure 1B). Three drugs (alectinib, lenvatinib, and isavuconazole) had R_1 values > 1.1, however, when evaluated clinically or using PBPK modeling, none of them were expected to be significant clinical inhibitors of CYP2C8. In contrast, two drugs with R_1 < 1.1, namely lesinurad and rolapitant significantly increased the exposure of coadministered repaglinide, a CYP2C8 probe substrate, by approximately 30%. The remaining drugs with R_1 values less than the cut-off were not evaluated clinically; however, based on the in vitro study results, concomitant use of the combination drug lumacaftor (also an in vitro inducer of CYP2C8) and ivacaftor with CYP2C8 substrates may alter the exposure of these substrates (FDA, 2015ad). For CYP2C9, six NMEs and six active metabolites (including two from prodrugs) inhibited CYP2C9 in vitro (Figure 1B); however, no clinical inhibition was observed when these drugs were coadministered with CYP2C9 substrates, regardless of R_1 values. Similarly, for CYP2C19, among all of the NMEs with positive in vitro inhibition results (six drugs

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and five metabolites, including two from prodrugs, Figure 1B), only rolapitant was found to weakly inhibit CYP2C19 in vivo, although the interaction was not considered clinically meaningful. Finally, with regard to CYP2D6, three NMEs and one active metabolite from a prodrug had R_1 values > 1.1 and were evaluated clinically (Table 3), two of which, panobinostat and rolapitant, were found to be weak-to-moderate inhibitors of CYP2D6. On the basis of these study results, concurrent use of rolapitant with CYP2D6 substrates with an NTI is contraindicated (e.g. thioridazine) or should be avoided (e.g. pimozide). Similarly, concomitant use of panobinostat with sensitive CYP2D6 substrates or CYP2D6 substrates with an NTI should be avoided. In both cases, if concomitant use of CYP2D6 substrates is unavoidable, it is recommended to monitor patients for adverse reactions (FDA, 2015s; FDA, 2015ad).

In terms of enzyme induction potential, 27 (82%) NMEs were assessed using human hepatocytes, and 12 drugs were found to induce DME expression or activity, or activate pregnane X receptor (PXR) to some extent (Table 4): alectinib (CYP2B6 and CYP3A4), cangrelor (CYP2C9 and CYP3A4/5), cobimetinib (CYP3A4), daclatasvir (CYP2B6 and CYP3A4), deoxycholic acid (CYP1A2), lenvatinib (CYP3A4), lesinurad (CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5), lumacaftor (CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5), osimertinib (CYP1A2, CYP3A4/5, and PXR), rolapitant (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5), selexipag (CYP3A4), and tenofovir alafenamide fumarate (PXR). Isavuconazole also showed some induction of CYP1A2, CYP2B6, CYP2C8, and CYP3A4/5. For most of the drugs, however, these interactions were considered unlikely to have any clinical relevance, and in vivo, only three NMEs showed clinical induction of P450s: lumacaftor (dosing regimen unavailable) was found to strongly induce CYP3A, causing an 80% decrease in the AUC of the coadministered ivacaftor, a sensitive substrate of CYP3A; isavuconazole (200 mg orally once daily administered as the prodrug isavuconazonium sulfate) was a weak inducer of both CYP2B6 (bupropion AUC ratio = 0.58, C_{max} ratio = 0.69) and CYP3A (ritonavir AUC ratio = 0.69, C_{max} ratio unavailable; lopinavir AUC ratio = 0.73, C_{max} ratio unavailable); and lesinurad (400 mg orally once daily) weakly induced CYP3A (amlodipine AUC ratio = 0.58, C_{max} ratio = 0.61). On the basis of these results, it is not

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recommended to administer lumacaftor/ivacaftor (as the combination drug ORKAMBI) with sensitive CYP3A substrates or CYP3A substrates with an NTI because of the risk of induction (FDA, 2015ad). Similarly, it is suggested to consider a dose increase of bupropion and use lopinavir/ritonavir with caution when coadministered with isavuconazonium sulfate, and to monitor patients for a potential reduction in efficacy of sensitive CYP3A substrates with coadministration of lesinurad (FDA, 2015g; FDA, 2015ag). Interestingly, almost all the in vitro inducers also showed inhibition of the same P450 enzyme (Table 3). For example, rolapitant was found to increase CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 activities up to 3.0-fold at 10 μM in human hepatocytes and to also inhibit these enzymes in HLMs with IC_{50} values of 23, 9.6, 8.7, and 41 μM, respectively; it was also a possible TDI of CYP3A4/5. In vivo, overall inhibition of CYP2C8 and CYP2C19 was observed with a 30-50% increase in the exposure to the respective substrates repaglinide and omeprazole, whereas rolapitant coadministration had no significant effects on the PK of CYP2C9 and CYP3A probe substrates tolbutamide and midazolam. Similarly, daclatasvir induced CYP3A4 mRNA expression by 27.3-fold and also inhibited CYP3A4/5 (IC_{50} = 11.0 and 31.8 μM for substrates testosterone and midazolam, respectively). However, when tested in vivo with the probe substrate midazolam, daclatasvir had no significant effect on CYP3A. Another interesting example is isavuconazole, which was shown to induce CYP2C8 and CYP3A4/5 activities in vitro, and to inhibit these two enzymes as well. In vivo, coadministration of the prodrug isavuconazonium sulfate (dosing regimen unavailable) did not affect the PK of the coadministered CYP2C8 probe substrate repaglinide; however, significant increases in the exposure of known substrates of CYP3A were observed, including tacrolimus (AUC ratio = 2.25, C_{max} ratio = 1.42), midazolam (AUC ratio = 2.03, C_{max} ratio = 1.72), sirolimus (AUC ratio = 1.84, C_{max} ratio = 1.65), atorvastatin (AUC ratio = 1.40, C_{max} ratio unavailable), and cyclosporine (AUC ratio = 1.30, C_{max} ratio unavailable), whereas significant decreases in the exposure of ritonavir (AUC ratio = 0.69, C_{max} ratio unavailable) and lopinavir (AUC ratio = 0.79, C_{max} ratio unavailable), also metabolized by CYP3A, were observed. Finally, no effect was observed on oral contraceptives or prednisone, suggesting that the net effect (inhibition or induction) of isavuconazole on CYP3A was substrate dependent. Similar to the NDA approvals in previous years (Yu et al., 2014; Yu

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et al., 2016), nuclear receptors were not commonly investigated. Indeed, only five NMEs (cobimetinib, ivabradine, osimertinib, sonidegib, and tenofovir alafenamide fumarate) were evaluated for PXR activation and one (tenofovir alafenamide fumarate) for aryl hydrocarbon receptor activation together with P450 induction assessment (except ivabradine, which was only evaluated for PXR activation). As a result, osimertinib and tenofovir alafenamide fumarate showed PXR activation. However, in contrast to osimertinib, which was also found to induce CYP3A activity, no induction of CYP3A mRNA expression (activity not measured) was observed in human hepatocytes with tenofovir alafenamide fumarate at concentrations up to 100 μM. Interestingly, among the three drugs without PXR activation, cobimetinib was found to induce CYP3A4 mRNA expression by 9.1-fold at 10 μM, indicating induction of CYP3A4 independent of PXR regulation. In addition to P450s, lenvatinib, panobinostat, and tenofovir alafenamide fumarate were investigated for their induction potential of UGTs (including UGT1A1/4/9 and UGT2B7). Induction of transporters was also evaluated in two cases: panobinostat for the induction of P-gp and multidrug resistance-associated protein 2 (MRP2), and tenofovir alafenamide fumarate for P-gp. However, no induction was observed in these pre-clinical studies.

In summary, when NMEs were evaluated as substrates of DMEs in vitro, the most represented enzyme was CYP3A, involved in the metabolism of 22 of 33 NMEs (64%). However, only 12 of these NMEs (36%) were confirmed to be clinical substrates of CYP3A. As perpetrators, 21 drugs showed some inhibition and/or induction towards at least one enzyme in vitro, but only six were found to affect significantly the exposure of clinical probe substrates (AUC or C_{max} ratio ≥ 1.25 or ≤ 0.8).

Transport and Transporter-Mediated DDIs

Out of the 33 NDA approval packages released by the FDA in 2015, 25 (76%) contained in vitro transport data involving a total of 37 compounds (25 parent drugs plus 12 metabolites, including three metabolites of prodrugs). In the past three years, there has been a consistent increase in the number of NDA approval packages which include in vitro transport data, reflective of the increased emphasis on in vitro transporter assays by the regulatory agencies (EMA, 2012; FDA, 2012; PMDA, 2014). Notably, this year for one

NDA, lesinurad, a treatment for hyperuricemia associated with gout, inhibition of a urate transporter urate anion exchanger 1 (URAT1) is the mechanism of action (clinical trials of which are not included in the following statistics). To follow up on the in vitro studies, seven NMEs were tested as in vivo substrates of P-gp, BCRP, organic anion-transporting polypeptides OATP1B1/3, organic cation transporter OCT2, organic anion transporter OAT3, or MRP2. More than 20 clinical trials were performed using the NME as the victims with clinical inhibitors or inducers, resulting in nine positive studies (AUC ratio $\geq$ 1.25 or $\leq$ 0.8). Similarly, more than 20 clinical studies were performed to investigate 10 NMEs as in vivo inhibitors of P-gp, BCRP, OATP1B1/3, OAT1/3, and OCT1 using the NME as the perpetrator, with 10 showing positive results.

Overall, the number of transporters tested in in vitro assays increased with respect to previous years (16 in 2013 and 19 in 2014), with 21 individual transporters tested: P-gp, BCRP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT2, OAT3, OAT4, OCT1, OCT2, OCT3, multidrug and toxin extrusion proteins MATE1 and MATE2-K, bile salt export pump (BSEP), MRP2, MRP4, URAT1, sodium-taurocholate co-transporting polypeptide (NTCP), apical sodium-dependent bile acid transporter (ASBT), and sodium-phosphate transporter NPT1. Similar to 2014, almost 400 transporter assays were described within the approval packages, with a majority of the assays performed using the NME as an inhibitor. More than one third of the in vitro substrate assays were positive, while half of the in vitro inhibition assays were positive.

As was the case in 2013 and 2014, P-gp was the most tested transporter in vitro in terms of substrates (30 out of 37 NMEs including parent drugs and metabolites), as well as had the most positive interactions – 19 NMEs, comprising 15 parent drugs and four metabolites (Figure 2A). Of the 15 parent drugs identified as in vitro substrates (alectinib, cobimetinib, daclatasvir, edoxaban, eluxadoline, ixazomib, ivabradine, lenvatinib, osimertinib, palbociclib, panobinostat, sacubitril, selexipag, tenofovir alafenamide fumarate, trabectedin, and uridine triacetate), six were tested as in vivo substrates; with all six showing positive interactions, four of which had the victim AUC ratios $\geq$ 2. The largest interaction identified was when

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ivabradine was coadministered with ketoconazole (200 mg orally once daily; ivabradine AUC ratio = 7.70, C_{max} ratio = 3.60), although this effect was likely due to CYP3A inhibition as well, as discussed in the metabolism section, ivabradine being also a substrate of CYP3A and ketoconazole being a strong CYP3A inhibitor. Likewise, the interaction between daclatasvir and simeprevir (150 mg orally once daily; daclatasvir AUC ratio = 2.20; C_{max} ratio = 1.60) could also be, at least partially, mediated by CYP3A (simeprevir has been shown to weakly inhibit intestinal CYP3A) (FDA, 2015f). Interestingly, cyclosporine, also a P-gp inhibitor, had no clinically relevant effect on daclatasvir PK. The next largest interactions were when prodrug tenofovir alafenamide fumarate was coadministered with cobicistat (150 mg orally once daily; tenofovir alafenamide fumarate AUC ratio = 2.65 and C_{max} ratio = 2.80; active metabolite tenofovir AUC_{tau} ratio = 3.31, C_{max} ratio = 3.34) and selexipag was coadministered with lopinavir/ritonavir (dosing regimen unavailable; selexipag AUC ratio = 2.00; C_{max} ratio = 2.00), although these interactions could be due to inhibition of other transporters in addition to P-gp (BCRP and OATP1B1/3, and OATP1B1/3, respectively). Edoxaban was evaluated with seven different P-gp inhibitors including amiodarone (400 mg orally once daily), cyclosporine (500 mg orally single dose), dronedarone (400 mg orally twice daily), erythromycin (500 mg orally four times daily), ketoconazole (400 mg orally once daily), quinidine (300 mg orally three times daily) and verapamil (240 mg orally once daily), all of which increased edoxaban AUC and C_{max} by 40-90%. Lenvatinib was evaluated in vivo with both ketoconazole and rifampin as the inhibitors, and while ketoconazole had no effect, rifampin (600 mg orally single dose) had a small effect on lenvatinib exposure (AUC ratio = 1.30, C_{max} ratio = 1.32). Regarding in vivo induction of P-gp, two NMEs were evaluated, edoxaban and lenvatinib, using multiple doses of rifampin. For edoxaban, the AUC ratio was 0.60, with no effect of rifampin on C_{max}; whereas for lenvatinib, the AUC ratio was 0.83 and the C_{max} ratio was 0.98, and there was a 23% increase in lenvatinib clearance.

Roughly an equal number of NMEs were evaluated in vitro as substrates of OATP1B1, OATP1B3 and BCRP (16, 15, and 16, respectively), and approximately two thirds were evaluated against OAT1/3,

OCT1/2 and MRP2, with less than half of these interactions showing a positive result. As mentioned above, in addition to P-gp, the interaction of tenofovir alafenamide fumarate with cobicistat may also be mediated by OATP1B1/3 as well BCRP, while the selexipag interaction with lopinavir/ritonavir may also be mediated by OATP1B1/3. In addition, the interaction between edoxaban and cyclosporine may be partially mediated by OATP1B1, as the main circulating metabolite of edoxaban, M4, is a substrate of OATP1B1, although the parent compound is not. The largest interaction mediated by OATP1B1, however, was observed when eluxadoline was coadministered with cyclosporine (600 mg single dose; eluxadoline AUC ratio = 4.20, C_{max} ratio = 6.80). Due to the large increase in eluxadoline exposure, it is recommended to reduce the dose of eluxadolin when coadministered with OATP1B1 inhibitors as well as to monitor for adverse events (FDA, 2015u). A smaller interaction was observed when eluxadoline was coadministered with the OAT3/MRP2 inhibitor probenecid (500 mg single dose; eluxadoline AUC ratio = 1.28, C_{max} ratio = 1.19).

When the NMEs were evaluated as inhibitors, the seven transporters explicitly mentioned in the FDA guidance document (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2) showed roughly equal representation, with the exception of P-gp, for which more NMEs were tested. The most NMEs were shown to be in vitro inhibitors of OATP1B1, followed by BCRP, then OATP1B3 (Figure 2B). Of the 11 NMEs and three metabolites that showed in vitro inhibition of either OATP1B1 or OATP1B3, half of the parent drugs and all the metabolites had C_{max}/IC_{50} values less than the FDA cut-off value of 0.1 (Table 5). One NME, deoxycholic acid, had C_{max}/IC_{50} values slightly above the cut-off value (0.14 for OATP1B1 and 0.11 for OATP1B3), however the subsequently calculated R value was less than the FDA cut-off value of 1.25, therefore no clinical study was conducted. For panobinostat, no IC_{50} values were presented in the NDA approval package, however the R value ($R = 1 + (f_u \times I_{in,max}/ IC_{50})$ was equal to 1, therefore no clinical study was triggered for this NDA either. For the remaining six drugs, the C_{max}/IC_{50} values exceeded the FDA cut-off value, and clinical studies were performed with either atorvastatin or rosuvastatin (both known OATP substrates), with the exception of lenvatinib, for which the clinical effect

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was not investigated. As a result, daclastasvir (60 mg orally once daily) and eluxadoline (100 mg single dose) were found to increase the AUC and C_{max} of coadministered rosuvastatin by 40-47% and 18-84%, respectively; isavuconazonium sulfate and sacubitril (dosing regimen unavailable for both) increased atorvastin AUC 30-40% and C_{max} 5-75%, whereas the coadministration of lesinurad had no effect on atorvastatin PK (atorvastatin AUC ratio = 1.01; C_{max} ratio = 1.17).

Eleven NMEs and three metabolites were shown to be in vitro inhibitors of BCRP, with three NMEs (cariprazine, lesinurad, and selexipag) not triggering clinical trials based on in vitro data ($[I]_1/IC_{50} < 0.1$ and/or $[I]_2/IC_{50} < 10$, where $[I]_1$ is total C_{max} representing systemic exposure and $[I]_2$ is the highest dose in mol/250 mL to represent intestinal exposure). For seven of the remaining eight parent compounds, both the $[I]_1/IC_{50}$ and $[I]_2/IC_{50}$ values were greater than the FDA cut-off values, and for osimertinib, only the $[I]_2/IC_{50}$ value was greater (Table 6). Clinical studies were undertaken for brexpiprazole, daclatasvir, isavuconazonium sulfate, and rolapitant. No effect was observed with brexpiprazole (rosuvastatin as the victim drug) or isavuconazonium sulfate (methotrexate as the victim drug). Both daclatasvir and rolapitant caused changes in the victim PK, with the larger effect by rolapitant (200 mg single dose) when coadministered with sulfasalazine (sulfasalazine AUC ratio = 2.18, C_{max} ratio = 2.38). Therefore, increased plasma concentration of BCRP substrates with an NTI may result in potential adverse reactions with concurrent use of rolapitant, and patients should be monitored for adverse reactions related to the concomitant drug (FDA, 2015s). The effect of daclatasvir (60 mg orally once daily) on rosuvastatin exposure was also considered clinically significant (rosuvastatin AUC ratio = 1.47, C_{max} ratio = 1.84). Note that, as mentioned above, inhibition of OATP1B1/3 may also be involved in the interaction of daclatasvir and rosuvastatin. For the remaining four NMEs, the in vitro data suggested possible in vivo inhibition of BCRP; however, no clinical studies were undertaken. A clinical study was requested for osimertinib as a PMR to evaluate the effect of repeated doses of osimertinib on the PK of a probe substrate of BCRP. Similarly, it was recommended to conduct such studies for alectinib in comments from the FDA reviewers. It is worth noting that while four clinical trials were undertaken to study

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inhibition of BCRP, three different victim drugs were used, namely methotrexate, rosuvastatin, and sulfasalazine, highlighting the need for the identification of an appropriate BCRP probe substrate (Lee et al., 2015).

Concerning inhibition of P-gp, a total of 14 NMEs were shown to be in vitro inhibitors, comprising nine parent drugs and five metabolites. For two NMEs, cariprazine and lesinurad, no clinical studies were triggered based on the in vitro inhibition data (Table 7). Interestingly, four NMEs (brexpiprazole, edoxaban, ivabradine, and sacubitril) either did not inhibit P-gp in vitro or inhibition was deemed not clinically relevant ($[I]_1/IC_{50} < 0.1$ and $[I]_2/IC_{50} < 10$), however the sponsor still performed in vivo clinical studies with a P-gp probe substrate. Indeed, brexpiprazole had no effect on fexofenadine PK, and edoxaban and sacubitril had no effect on digoxin PK. In the case of ivabradine, while the parent compound did not inhibit P-gp in vitro, the metabolite S18982 showed minor inhibition of P-gp, with an IC_{50} of 5.3 μM. However, this is at least two orders of magnitude greater than the total plasma concentration, therefore unlikely to cause systemic inhibition, which was confirmed in an in vivo clinical trial, where ivabradine had no effect on digoxin PK. In vitro data for the remaining six NMEs (daclatasvir, flibanserin, isavuconazonium sulfate, rolapitant, alectinib, and uridine triacetate) showed that at least one of the $[I]/IC_{50}$ values was greater than the FDA cut-off. When evaluated clinically with the P-gp probe substrate digoxin, daclatasvir (60 mg orally once daily), flibanserin (100 mg orally once daily), isavuconazonium sulfate (200 mg orally once daily), and rolapitant (180 mg orally single dose) all showed significant increases in the exposure to digoxin, with AUC ratios of 1.27, 1.93, 1.25, and 1.27, respectively, and C_{max} ratios of 1.65, 1.46, 1.33, and 1.67, respectively. These results were all reflected in the labels (FDA, 2015h; FDA, 2105a; FDA, 2015g; FDA, 2015s). Interestingly, the largest effect was observed with flibanserin (digoxin AUC ratio = 1.93, C_{max} ratio = 1.46), although inhibition of P-gp in vitro was quite weak, reducing the efflux ratio of digoxin from 8.15 to only 3.44 at the highest concentration tested. For the remaining two NMEs (alectinib and uridine triacetate), although one or both of the $[I]/IC_{50}$ values exceeded the FDA cut-off, no clinical studies were performed. In the case of prodrug

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uridine triacetate, which is rapidly converted to uridine (no inhibition of P-gp in vitro), due to the high gut concentrations of uridine triacetate (approximately 37 mM), the sponsor acknowledged that an interaction at the gut level cannot be ruled out; however, no in vivo P-gp inhibition study was conducted.

Finally, two clinical trials were performed to assess whether or not lesinurad was an in vivo inhibitor of OAT1/3 or OCT1, as in vitro lesinurad inhibited all three transporters with IC_{50} values < 5 μM. To investigate the inhibition potential of OAT1/3, lesinurad (400 mg single dose) was coadministered with furosemide. Although a decrease in furosemide plasma exposure (AUC ratio = 0.69, C_{max} ratio = 0.49) and a 45% increase in its clearance was observed, the renal clearance was not decreased in the presence of lesinurad. Additionally, there was no effect on the diuretic effects of furosemide; therefore, the sponsor concluded that lesinurad was not an in vivo inhibitor of OAT1/3 (FDA, 2015ag). To investigate OCT1 inhibition, lesinurad was coadministered with metformin and no effect was observed (metformin AUC ratio = 1.03; C_{max} ratio = 1.06).

In summary, 18 NMEs were shown to be substrates of one or more transporter in vitro and seven were tested in vivo. All seven NMEs showed at least one positive interaction, with two interactions likely also due to CYP3A inhibition, and three likely due to more than one transporter. Regarding inhibition, 19 NMEs were in vitro inhibitors of at least one transporter, 10 of which were studied in vivo. Six NMEs showed positive interactions in seven studies, with all of the exposure changes being less than 2-fold, except for rolapitant and sulfasalazine (mediated by BCRP), for which the AUC and C_{max} ratios of sulfasalazine were both > 2. As in the previous two years, while a majority of the NMEs tested were shown to be either substrates or inhibitors of one or more transporter in vitro, this often failed to translate into positive in vivo interactions, indicative of the need for more research into transporter in vitro to in vivo extrapolation.

PGx Studies

For eight NMEs (brexpiprazole, cariprazine, edoxaban, eluxadoline, flibanserin, lenvatinib, lesinurad, and panobinostat), the effects of genetic variants of the primary enzymes (including CYP1A2, CYP2A6,

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CYP2C9, CYP2C19, CYP2D6, and CYP3A5) and transporter (OATP1B1) on the PK of each drug were evaluated. This is a significant increase compared with four NMEs in 2014 and two NMEs in 2013 (Yu et al., 2014; Yu et al., 2016). Three NMEs, brexpiprazole, flibanserin, and lesinurad, had PGx study results highlighted in the labeling. Brexpiprazole, which is metabolized by both CYP3A4 (47%) and CYP2D6 (43%), displayed a significant effect of CYP2D6 polymorphism on its disposition. Indeed, brexpiprazole AUC was about 2-fold higher in CYP2D6 poor metabolizers (PMs) compared with extensive metabolizers (EMs) and intermediate metabolizers (IMs). In addition, concurrent administration of the strong CYP3A inhibitor ketoconazole (200 mg orally twice daily) and the strong CYP2D6 inhibitor quinidine (324 mg orally once daily) increased brexpiprazole exposure to a similar level in CYP2D6 EMs and IMs (ketoconazole AUC ratio = 2.17, C_{max} ratio = 1.18; quinidine AUC ratio = 2.03, C_{max} ratio = 1.12.). The worst case scenario (maximum exposure) was estimated based on a population PK analysis, which predicted approximately a 5-fold increase in brexpiprazole AUC when CYP2D6 EMs were administered with both strong CYP2D6 and CYP3A inhibitors, or when CYP2D6 PM subjects were administered with strong CYP3A inhibitors. On the basis of these results, it is recommended to reduce the dose of brexpiprazole by half or quarter accordingly (FDA, 2015p). A PGx study with flibanserin, a drug primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19, showed a 34% and 47% increase in flibanserin AUC and C_{max}, respectively, in CYP2C19 PM subjects compared to CYP2C19 EM subjects, confirming that flibanserin is partially metabolized by CYP2C19. It is mentioned in the labeling that increases in flibanserin exposure in CYP2C19 PMs may increase risk of hypotension, syncope, and central nervous system depression (FDA, 2015a). This is consistent with the results of an interaction study, where coadministration of flibanserin with fluconazole (200 mg orallyonce daily), a strong CYP2C19 inhibitor and a moderate CYP3A inhibitor, resulted in a larger change in flibanserin exposure (AUC ratio = 6.41, C_{max} ratio = 2.11), compared with coadministration of ketoconazole (400 mg orally once daily; AUC ratio = 4.61, C_{max} ratio = 1.84), a strong CYP3A inhibitor. Based on the interaction study results with fluconazole, the label suggests to “discuss the use of a strong CYP2C19 inhibitor with the patients when prescribing flibanserin” (FDA, 2015a). In contrast, no significant changes in flibanserin PK

were observed in CYP2C9 PM or CYP2D6 PM/IM/UM subjects compared with EMs, indicating minimal involvement of these enzymes in flibanserin metabolism. As for lesinurad, which is primarily metabolized by CYP2C9, a PGx study showed that subjects with a CYP2C9 PM status (i.e., CYP2C9*3/*3) who received lesinurad had an approximately 1.8-fold increase in lesinurad exposure relative to CYP2C9 EMs (i.e., CYP2C9*1/*1). It is recommended that lesinurad be used with caution in CYP2C9 PMs, and in patients taking moderate inhibitors of CYP2C9 (FDA, 2015ag).

PBPK Modeling and Simulations

The use of PBPK simulations for the prediction of DDIs has steadily increased in recent years (Sager et al., 2015). Consistent with this trend, among the drugs approved in 2015, PBPK modeling and simulation was used in at least one DDI prediction for seven NMEs, namely alectinib, aripiprazole, cobimetinib, lenvatinib, osimertinib, panobinostat, and sonidegib. In place of dedicated clinical studies, the DDI modeling and simulation results for four of these drugs, cobimetinib, lenvatinib, panobinostat, and sonidegib, were used directly to inform dosing recommendations (FDA, 2015m; FDA, 2015j; FDA, 2015o; FDA, 2015z). As a comparison, six NMEs in 2014 and five NMEs in 2013 contained PBPK modeling and simulation data in the NDAs (Yu et al., 2016).

Cobimetinib, panobinostat, and sonidegib are all extensively metabolized by CYP3A. For these three drugs, the effect of strong inhibition of CYP3A on their plasma exposure was investigated clinically with coadministration of ketoconazole or itraconazole, whereas the DDI risk with moderate inhibitors was evaluated using PBPK simulations. Interestingly, the clinical evaluation of the effect of strong CYP3A inducers was only conducted for sonidegib (AUC ratio = 0.28, C_{max} ratio = 0.46 when coadministered with rifampin 600 mg orally once daily), whereas PBPK simulations were used to predict the effect of rifampin (600 mg orally once daily) coadministration on cobimetinib (predicted AUC ratio = 0.17, C_{max} ratio = 0.37) and panobinostat (predicted AUC ratio = 0.35, C_{max} ratio = 0.43). Additionally, the effects of the moderate CYP3A inducer efavirenz on cobimetinib and sonidegib exposure were also assessed using PBPK simulations. In all cases, PBPK modeling results were used to support dosing recommendations as

an alternative for clinical studies. For example, for cobimetinib, it was predicted that coadministration with the strong inducer rifampin (600 mg orally once daily) or moderate inducer efavirenz (600 mg orally once daily) may decrease cobimetinib exposure by 83% and 73%, respectively. Due to the possibility of reduced efficacy of cobimetinib, the product label recommends avoiding concomitant administration with both strong and moderate inducers of CYP3A (FDA, 2015z). On the other hand, coadministration of cobimetinib with the moderate CYP3A inhibitors erythromycin (500 mg orally three times daily) or diltiazem (1200 mg orally twice daily) was predicted to cause a 3- to 4-fold increase in cobimetinib exposure, whereas coadministration of fluvoxamine, a weak inhibitor of CYP3A, was predicted to have no effect on cobimetinib plasma levels. Consequently, it is recommended to avoid concomitant use of cobimetinib with strong or moderate CYP3A inhibitors (FDA, 2015z). Finally, for panobinostat, PBPK model-based simulations predicted a 65% decrease in panobinostat AUC when coadministered with the strong inducer rifampin (600 mg orally once daily). As a result, the label recommends avoiding coadministration of panobinostat with strong CYP3A inducers (FDA, 2015j).

PBPK simulations were also used to evaluate the DDIs with probe substrates of DMEs when NMEs were considered as perpetrators. For example, panobinostat was found to be a time-dependent inhibitor of CYP3A in vitro. However, PBPK model-based simulations predicted that coadministration of panobinostat with midazolam (a sensitive CYP3A substrate) would not alter midazolam AUC, and therefore CYP3A activity, to any clinically significant extent (midazolam AUC increase < 10%). A clinical trial to investigate the DDI between panobinostat and midazolam has still been proposed by the sponsor (FDA, 2015j). Similarly, for lenvatinib, which was shown to be a TDI of CYP3A and a direct inhibitor of CYP2C8 in vitro, PBPK modeling predicted no effect of lenvatinib on the exposure of the CYP3A substrate midazolam or the CYP2C8 substrate repaglinide. In the case of lenvatinib, the predicted results were determined to be adequate to support lenvatinib labeling regarding the lack of CYP inhibition potential (FDA, 2015m). Finally, PBPK modeling and simulations were used to evaluate the effect of pH modifiers on the absorption of panobinostat, and it was predicted that coadministration with drugs that elevate gastric pH would not alter the absorption of panobinostat.

Clinically Significant Drug-Drug Interactions

For the present analysis, all positive studies (AUC ratio ≥ 1.25 for inhibition and ≤ 0.8 for induction) were analyzed and DDIs yielding an AUC ratio of 2 (for inhibition) or 0.5 (for induction) were highlighted, as a 2-fold change in drug exposure often triggers dosing recommendations. In order to also recognize drugs with a narrower therapeutic range, studies with drug exposure ratios less than 2-fold but triggering labeling recommendations were also identified. Overall, 95 positive in vivo DDI studies were observed and involved 21 of the 33 NMEs (64%), with the NMEs being mainly victim drugs. Clinically significant inhibition and induction results (exposure ratio of 2 and/or labeling recommendations; n = 78 studies) observed with NMEs as victims or perpetrators are presented in Tables 8 (inhibition) and 9 (induction).

For inhibition studies, a total of 68 DDI evaluations (including three PBPK simulations) showed an exposure change of more than 25% of the substrate, with NMEs being victims or inhibitors. Among them, about 80% of the results were reflected in the labeling, half of which had AUC ratios ≥ 2, and half with AUC ratios of 1.25-2. As expected, all of the DDI results that were not highlighted in the labeling were those with AUC ratios < 2. A majority of the NMEs (n = 18) were victims, whereas nine NMEs were perpetrators, with seven NMES being both. Two thirds of the clinical interactions were due to inhibition of CYP3A. Of note, half of the NMEs that were CYP3A substrates were also transported by P-gp and/or BCRP, therefore inhibition of these transporters may also contribute to the overall observed interactions. Other P450s, such as CYP2C9, CYP2C19, and CYP2D6 were the next commonly involved enzymes in the clinical DDIs.

When NMEs were considered as victim drugs, the largest change in drug exposure among clinical inhibition interactions was observed with ivabradine. As discussed previously, ivabradine is extensively metabolized by CYP3A and a substrate of P-gp, and coadministration of the strong CYP3A/P-gp inhibitor ketoconazole (200 mg orally once daily) increased ivabradine AUC and C_{max} by 7.7- and 3.6-fold, respectively. Similar results were observed with concomitant administration of josamycin (dosing regimen unavailable), also considered a strong CYP3A inhibitor. According to the ivabradine product

label, concomitant use of strong CYP3A inhibitors with ivabradine is contraindicated (FDA, 2015f). On the other hand, when NMEs are considered as inhibitors, the most affected enzymes were CYP2D6, CYP3A, and UGTs. The largest clinical inhibition was observed with coadministration of rolapitant (200 mg orally single dose), which increased the exposure to dextromethorphan (a CYP2D6 probe substrate) by 2.6-fold, indicating that rolapitant is a moderate inhibitor of CYP2D6. Interestingly, two NMEs, isavuconazole and palbociclib, inhibited CYP3A with up to 2-fold increases in the exposure of coadministered CYP3A substrates, and were also sensitive substrates of CYP3A. Almost half of the observed clinical interactions were mediated primarily by inhibition of transporters, including P-gp, BCRP, and OATP1B1/3. Several NMEs were also found to inhibit both enzymes and transporters. For example, isavuconazole (administered as the prodrug isavuconazonium sulfate) inhibited CYP3A (midazolam AUC ratio = 2.03, C_{max} ratio = 1.72), UGTs (mycophenylate mofetil AUC ratio = 1.35, C_{max} ratio = 0.89), and P-gp (digoxin AUC ratio = 1.25, C_{max} ratio = 1.33).

Regarding induction data (Table 9), a total of 27 DDI evaluations (including four PBPK simulations) showed a substrate exposure decrease of more than 20%, with NMEs being victims or inducers, and nearly all the results were highlighted in the respective drugs' labeling. The largest induction interaction effect was observed with isavuconazole as the victim drug. Coadministration of the strong inducer rifampin (600 mg orally once daily) almost completely abolished the exposure of isavuconazole (a 97% decrease in AUC). According to the product label, concomitant use of isavuconazonium sulfate with strong CYP3A inducers is contraindicated (FDA, 2015g). Significant inductions were almost all related to the NMEs as victim drugs, and consistent with the inhibition interaction results, involved primarily induction of CYP3A by the known inducer rifampin, except for lesinurad and edoxaban, for which induction of CYP2C9 and P-gp, respectively, was the main mechanism. A total of 15 NMEs were affected by induction interactions as victims, whereas only three NMEs were found to be clinical inducers: isavuconazole (CYP2B6 and CYP3A4), lesinurad (CYP3A), and lumacaftor (CYP3A).

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Finally, for transporter-based clinical interactions, there were 19 inhibition interactions with over a 1.25-fold increase in substrate exposure and one induction interaction with more than a 20% decrease in substrate exposure that could be explained predominantly by alteration of transport. Four NMEs (edoxaban, eluxadoline, selexipag, and tenofovir alefenamide fumarate) were victims of drug interactions in which transporters were the main contributor to the underlying mechanism. Edoxaban was found to be sensitive to both inhibition of P-gp and OATP1B1 by multiple inhibitors (30-90% increase in exposure) and induction by rifampin (a 40% decrease in exposure), a known inducer of multiple enzymes and transporters, including P-gp. When NMEs were evaluated as perpetrators, about one third of the clinical drug interactions were mediated by transporters. The highest exposure change was observed with coadministration of rolapitant (200 mg orally single dose), which increased sulfasalazine AUC by 2.2-fold and C_{max} by 2.4-fold, indicating inhibition of intestinal BCRP. Four NMEs, namely daclatasvir (60 mg orally once daily), flibanserin (100 mg orally once daily), isavuconazole (200 mg orally once daily), and rolapitant (180 mg single dose), were found to inhibit P-gp, with increases of 25-93% in the exposure to digoxin (a P-gp substrate). Finally, eluxadoline was found to be both a victim (4.2-fold increase in AUC and 6.8-fold increase in C_{max} when coadministered with cyclosporine 600 mg single dose) and an inhibitor (100 mg single dose; increase in rosuvastatin AUC by 41% and C_{max} by 18%) of OATP1B1.

Overall, all clinical interactions with AUC ratios over 2-fold triggered labeling recommendations, with the exception of two interactions involving selexipag (inhibition by lopinavir/ritonavir, AUC ratio = 2) and alectinib (induction by rifampin, AUC ratio = 0.27). For both drugs, the exposure to the active moiety (selexipag metabolite ACT-333679 and alectinib and its metabolite M4 combined, respectively) was not significantly altered and no dose adjustment is needed.

In conclusion, approximately two thirds of the drugs analyzed had clinically significant DDIs, with a majority of these NMEs being victim drugs. As expected, and similarly to what was observed with NMEs approved in previous years, the underlying mechanism for a large number of these clinical interactions was inhibition or induction of CYP3A.

Hepatic and Renal Impairment Studies

Overall, the impact of HI and/or RI on drug exposure was evaluated for 22 (67%) out of 33 NMEs, which was similar to what was observed in previous years (Yu et al., 2014; Yu et al., 2016). Among the 16 NMEs evaluated for HI studies, 12 had an AUC ratio (impaired/control) ≥ 1.25 in HI patients (mild, moderate, and severe, Child-Pugh class A, B, and C, respectively) versus healthy controls, resulting in dosing recommendations, whereas four NMEs (cariprazine, parathyroid hormone, rolapitant, and tenofovir alafenamide fumarate) had AUC ratios < 1.25, however dosing recommendations were still advised in these populations according to the labeling (Table 10). In addition, although no dedicated HI study was conducted, ivabradine was contraindicated in patients with severe HI considering its extensive hepatic metabolism. For five NMEs (aletinib, cobimetinib, osimertinib, palbocilib, and trabectidin), a dedicated HI study has been requested as a PMR (Table 10). Among the 12 NMEs with systemic exposure increases ≥ 1.25-fold in HI patients, eight (brexpiprazole, flibanserin, isavuconazonium sulfate, ixazomib citrate, lenvatinib, lesinurad, panobinostat, and selexipag) are extensively metabolized by the liver, whereas the metabolism of eluxadoline is not clearly established. Among the other three NMEs, sacubitril and edoxaban are mainly eliminated via renal excretion, and lumacaftor is mainly eliminated unchanged by biliary excretion. The largest exposure increase (13.7-fold) was observed for eluxadoline in severe HI patients. Additionally, eluxadoline showed AUC ratios of 7.97 and 8.99 in mild and moderate HI patients, respectively. Based on these results, eluxadoline is contraindicated in patients with severe HI, and the dose should be reduced in patients with mild and moderate HI (FDA, 2015u). Other changes in exposure ranged from a 1.25-fold change in edoxaban metabolite M4 (active) AUC when administered in mild HI patients to a 4.5-fold increase in AUC for flibanserin in patients with mild HI, yielding specific labeling recommendations in both cases.

With regard to RI studies, nine out of the 16 NMEs evaluated showed AUC ratios ≥ 1.25 in renally impaired patients versus healthy controls, resulting in specific dosing recommendations, whereas one NME (parathyroid hormone) had AUC ratios < 1.25, however still reported dosing recommendations

(Table 11). For four NMEs, cariprazine, cholic acid, lumacaftor, and tipiracil, even though dedicated RI studies were not performed, dosing recommendations for patients with RI were provided. In addition, a PMR was requested to evaluate the effects of RI on the PK of eluxadaline. Among the nine NMEs with a systemic exposure was increased by ≥ 1.25-fold, six (avibactam, edoxaban, ixazomib citrate, sacubitril, sugammadex, and tenofovir alafenamide fumarate) are mainly eliminated via renal excretion, whereas brexpiprazole and lenvatinib are mainly eliminated by biliary excretion, and lesinurad is eliminated by both renal and hepatic routes. Avibactam displayed the largest change in exposure in RI patients, with 3.8-, 7.1-, and 20-fold increases in AUC in moderate, severe, and end-stage renal disease patients, respectively, with dose adjustment recommendations for all RI patients (FDA, 2015d). Other changes in exposure ranged from a 1.4-fold change in ixazomib AUC in patients with severe RI to a 17.2-fold increase in AUC for sugammadex when administered in patients with severe RI, causing specific labeling recommendations in both cases. Of note, all the results with AUC ratios ≥ 1.25 were reflected in the labeling, except for cangrelor, which showed 2.2- and 2.4- fold increases in AUC and C_{max}, respectively, in RI patients (CrCL 20-70 mL/min). However, further evaluations in phase III studies found no significant effect of renal function on cangrelor safety and efficacy, therefore no dose adjustment was needed for the use in RI patients (FDA, 2015ab).

Conclusion

The current mechanistic approach used during the drug development process of NMEs to assess the risk of PK-based DDIs provides a solid framework for translating the observed results of pre-clinical and clinical evaluations into actionable recommendations. Similar to what was observed in previous years, the detailed evaluation of DDI data contained in the 2015 NDAs showed that most of these drugs were extensively evaluated and their drug interaction profiles were well characterized, with a continued effort in transporter-based DDIs and PBPK modeling and simulations. Overall, when considered as victims, three NMEs (cobimetinib, isavuconazole, and ivabradine) were identified as sensitive clinical substrates of CYP3A (with changes in exposure greater than 5-fold when coadministered with a strong inhibitor),

whereas, as perpetrators, most clinical DDIs involved weak-to-moderate inhibition or induction, with only one NME (lumacaftor) considered as a strong CYP3A inducer.

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Figure 1. Quantitation of compounds acting as substrates (NMEs) or inhibitors (NMEs and metabolites) of drug metabolizing enzymes in vitro. (A) Phase I and II enzymes contributing to NME metabolism (B) DMEs inhibited by NMEs (open bars) and metabolites (filled bars) (C) DMEs induced by NMEs (open bars) and metabolites (filled bars). *Other phase II enzymes include SULT2A1, other SULTs, GSTs, and unspecified conjugation enzymes; others include epoxide hydrolase, nucleotidase, thymidine phosphorylase, and unspecified biotransformation enzymes.

Figure. 2. Quantitation of compounds acting as substrates (NMEs and metabolites) or inhibitors (NMEs and metabolites) of transporters in vitro. (A) Transporters involved in transport of NMEs (open bars) and metabolites (filled bars). (B) Transporters inhibited by NMEs (open bars) and metabolites (filled bars).

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Table 1. NDAs approved by the FDA in 2015 (ordered by approval date)

Compound Name	DDI	HI/RI	PBPK	PGx	Therapeutic Class	Approval Date (mm/dd)	Reference
Edoxaban	Y	Y	N	Y	Cardiovascular Drugs	1/8	(FDA, 2015q)
Palbociclib	Y	Y[a]	N	N	Cancer Treatments	2/3	(FDA, 2015k)
Lenvatinib	Y	Y	Y	Y	Cancer Treatments	2/13	(FDA, 2015m)
Panobinostat	Y	Y	Y	Y	Cancer Treatments	2/23	(FDA, 2015j)
(Ceftazidime and) avibactam	Y	Y[b]	N	N	Anti-Infective Agents	2/25	(FDA, 2015d)
Isavuconazonium sulfate[c]	Y	Y	N	N	Anti-Infective Agents	3/6	(FDA, 2015g)
Cholic acid	Y [d]	N	N	N	Metabolism disorder/endocrinology treatments	3/17	(FDA, 2015e)
Ivabradine	Y	Y	N	N	Cardiovascular Drugs	4/15	(FDA, 2015f)
Deoxycholic acid	Y[d]	N	N	N	Metabolism disorder/endocrinology treatments	4/29	(FDA, 2015l)
Eluxadoline	Y	Y[e]	N	Y	Gastrointestinal Agents	5/27	(FDA, 2015u)
Cangrelor	Y	Y[b]	N	N	Cardiovascular Drugs	6/22	(FDA, 2015ab)
Lumacaftor (and ivacaftor)	Y	Y[e]	N	N	Respiratory System Agents	7/2	(FDA, 2015ad)
Sacubitril[c] (and valsartan)	Y	Y	N	N	Cardiovascular Drugs	7/7	(FDA, 2015k)
Brexpiprazole	Y	Y	N	Y	Central Nervous System Agents	7/10	(FDA, 2015p)
Sonidegib	Y	Y[a]	Y	N	Cancer Treatments	7/24	(FDA, 2015v)
Daclatasvir	Y	Y	N	N	Anti-Infective Agents	7/24	(FDA, 2015j)

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Flibanserin	Y	Y	N	Y	Central Nervous System Agents	8/18	(FDA, 2015a)
Rolapitant	Y	Y[f]	N	N	Antiemetics	9/1	(FDA, 2015s)
Uridine triacetate[c]	Y	N	N	N	Metabolism disorder/endocrinology treatments	9/4	(FDA, 2015w)
Cariprazine	Y	Y[f]	N	Y[a]	Central Nervous System Agents	9/17	(FDA, 2015v)
(Trifluridine and) tipiracil	Y	Y[a]	N	N	Cancer Treatments	9/22	(FDA, 2015n)
Insulin degludec	N	Y	N	N	Hormones	9/25	(FDA, 2015r)
Aripiprazole lauroxil[c]	N	N	Y[g]	N	Central Nervous System Agents	10/5	(FDA, 2015c)
Patiromer	Y[d]	N	N	N	Antidotes	10/21	(FDA, 2015t)
Trabectedin	Y	Y[b]	N	N	Cancer Treatments	10/23	(FDA, 2015x)
(Elvitegravir, cobicistat, emtricitabine, and) tenofovir alafenamide fumarate sulfate[c]	Y	Y	N	N	Anti-Infective Agents	11/5	(FDA, 2015aa)
Cobimetinib	Y	Y[b]	Y	N	Cancer Treatments	11/10	(FDA, 2015z)
Osimertinib	Y[d]	Y[a]	Y	N	Cancer Treatments	11/13	(FDA, 2015ae)
Ixazomib citrate[c]	Y	Y[h]	N	N	Cancer Treatments	11/20	(FDA, 2015ac)
Alectinib	Y	Y[a]	Y	N	Cancer Treatments	12/11	(FDA, 2015b)
Sugammadex	Y	Y[b]	N	N	Antidotes	12/15	(FDA, 2015y)
Selexipag	Y	Y	N	N	Cardiovascular Drugs	12/21	(FDA, 2015af)
Lesinurad	Y	Y	N	Y	Antigout and Uricosuric Agents	12/22	(FDA, 2015ag)

N, studies not included in the NDA reviews; Y, studies included in the NDA reviews; Compounds in parentheses are not new molecular entities.

[a] – Only population PK data is available for both HI and RI, and therefore not included in this analysis

[b] – Only population PK data is available for RI, and therefore not included in this analysis

[c] – Prodrug

[d] – Only pre-clinical data is presented

[e] – Only population PK data is available for HI, and therefore not included in this analysis

[f] – Only population PK data is available for RI, and not included in this analysis; clinical data is available on for HI

[g] – PBPK modeling and simulations were used to support historical PK data under different clinical situations for DDIs, but not used to recommend dosage

[h] – Population PK data is presented for mild HI and mild/moderate RI; others are from clinical data

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Table 2. Enzymes and transporters involved in the NDA elimination pathways

Compound Name	Main Elimination Route	Enzymes Involved	Transporters Involved	Reference
Edoxaban	Minimal metabolism, 62% in the urine and 35% in the feces renal (primarily as parent in both)	Carboxyesterase 1, phase II conjugation, CYP3A	P-gp, OATP1B1	(FDA, 2015q)
Palbociclib	Metabolism, 74.1% in the feces and 17.5% in the urine (percentage of parent vs. metabolites not available)	CYP3A[a], SULT2A1	P-gp, BCRP	(FDA, 2015k)
Lenvatinib	Metabolism, 64% in the feces and 25% in the urine (parent < 2.5% overall in both)	Aldehyde oxidase, CYP3A4, other P450s (not specified), phase II enzymes like GSH conjugation and other biotransformation	P-gp, BCRP	(FDA, 2015m)
Panobinostat	Metabolism, 29-51% in the urine (parent < 2.5%) and 44-77% in the feces (parent < 3.5%),	CYP3A[a], CYP2D6, 2C19, UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B4	P-gp	(FDA, 2015j)
(Ceftazidime and) avibactam	Not metabolized in the liver, renal excretion, 97% in the urine (80-90% as parent)	None	OAT1, OAT3	(FDA, 2015d)
Isavuconazonium sulfate	Metabolism, 46% in the feces and 46% in the urine (active isavaconazole < 1%)	Esterases[a], CYP3A4[a], CYP3A5[a], UGTs	None	(FDA, 2015g)
Cholic acid	Joins the endogenous bile acid pool in the enterohepatic circulation mainly in conjugated forms. Any cholic	CYP3A4, UGT2A1 and UGT2A2[b]	BSEP, BCRP[b]	(Deo and Bandiera, 2008; Blazquez et al., 2012; Perreault et al., 2013; FDA,

	acid not absorbed will be excreted in the feces alone or as deoxycholic acid.			2015e)
Ivabradine	Metabolism, metabolites 37% in the urine and 47% in the feces (4% as parent in each)	CYP3A4[a]	P-gp	(FDA, 2015f)
Deoxycholic acid	Not metabolized, excreted in the feces as parent	None	BSEP	(FDA, 2015l)
Eluxadoline	Not metabolized, 82% in the feces and 0.12% in the urine (percentage of parent vs. metabolites not assessed)	None[c]	OAT3, OATP1B1, BSEP, MRP2	(FDA, 2015u)
Cangrelor	Metabolism in plasma, 58% in the urine and 35% in the feces	Nucleotidases[a]	N/T	(FDA, 2015ab)
Lumacaftor (and ivacaftor)	Not extensively metabolized, biliary excretion, 51% in the feces as parent	Mainly via oxidation and glucuronidation enzymes	N/T	(FDA, 2015ad)
Sacubitril (and valsartan)	Metabolism, 51.7-67.8% in the urine and 36.9-48.3% in the feces (mainly as active metabolite LBQ657)	Esterases[a]	P-gp; LBQ657: OATP1B1/3, OAT3	(FDA, 2015k)
Brexpiprazole	Metabolism, 46% in the feces (14% as parent) and 25% in the urine (parent < 1%)	CYP3A4[a], CYP2D6[a]	P-gp, BCRP	(FDA, 2015p)
Sonidegib	Metabolism, 70% in the feces and 30% in the urine	CYP3A[a]	None	(FDA, 2015o)
Daclatasvir	Metabolism, biliary excretion, 88% in the feces (53% as parent), 6.6% in the urine (primarily as parent)	CYP3A[a], CYP2C8	P-gp	(FDA, 2015h)
Flibanserin	Metabolism, 51% in the feces	CYP3A4[a], CYP2C19[a]	None[d]	(FDA, 2015a)

	and 44% in the urine			
Rolapitant	Metabolism, biliary excretion, 73% in the feces (mainly as parent)and 14% in the urine (primarily as metabolites)	CYP3A4[a]	None	(FDA, 2015s)
Uridine triacetate	Metabolism and catabolism, renal excretion	Esterases[a]	P-gp, nucleoside transporters	(FDA, 2015w)
Cariprazine	Metabolism, 40.1% in the feces and 20.8% in the urine (parent and active metabolites accounts for 6-8% overall in both)	CYP3A4[a], CYP2D6, glucuronidation and sulfation enzymes	None	(FDA, 2015x)
(Trifluridine and) tipiracil	Not metabolized, mainly renal excretion as parent, no mass balance study	None	N/T	(FDA, 2015n)
Insulin delgudec	Proteolytic degradation	N/T, mostly by proteolytic enzymes	N/T	(FDA, 2015r)
Aripiprazole lauroxil	Hepatic metabolism	Parent: esterase[a]- and water-mediated hydrolysis[a], aripiprazole: CYP3A4[a] and CYP2D6[a]	N/T	(FDA, 2015c)
Patiromer	Not absorbed or metabolized, entirely excreted in the feces	N/T (not likely to be metabolized)	N/T	(FDA, 2015t)
Trabectedin	Metabolism, 58% in the feces and 6% in the urine (negligible as parent in each)	CYP3A4[a], other P450s (not specified)	P-gp	(FDA, 2015x)
(Elvitegravir, cobicistat, emtricitabine, and) tenofovir	Metabolism, renal excretion (mainly as active metabolite tenofovir)	Cathepsin A[a], Carboxyesterase 1, CYP3A4 (minimal)	P-gp, BCRP, OATP1B1/3	(FDA, 2015aa)

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alafenamide fumarate				
Cobimetinib	Metabolism, 76% in the feces (6.6% as parent) and 18% in the urine (1.6% as parent)	CYP3A, UGT2B7	P-gp	(FDA, 2015z)
Osimertinib	Metabolism, 68% in the feces and 14% in urine (2% as parent overall in both)	CYP3A[a]	P-gp, BCRP	(FDA, 2015ae)
Ixazomib citrate	Metabolism, 62% in the urine (< 3.5% as parent) and 22% in the feces (mainly as active metabolite ixazomib)	CYP3A[a], CYP1A2, CYP2B6, CYP2C8, CYP2D6, CYP2C19, CYP2C9	P-gp	(FDA, 2015ac)
Alectinib	Metabolism, biliary excretion, 98% in the feces (84% as parent) and < 0.5% in the urine	CYP3A4[a], CYP2B6, CYP2C8, CYP2C9, CYP2D6	P-gp	(FDA, 2015b)
Sugammadex	Mainly renal excretion, metabolism (< 5%)	N/T (not likely to be metabolized by P450s or the liver)	N/T	(FDA, 2015y)
Selexipag	Metabolism, 93% in the feces and 12% in the urine	Carboxyesterase 1[a], CYP2C8[a], CYP3A4, UGT1A3, UGT2B7	P-gp, OATP1B1/3	(FDA, 2015af)
Lesinurad	Metabolism, 63% in the urine and 32% in the feces (64% as metabolites in both and 31% was excreted in urine as parent)	CYP2C9[a], CYP1A1, CYP2C19, CYP3A, epoxide hydrolase	OAT1/3, OATP1B1/3, OCT1, BCRP	(FDA, 2015ag)

N/T – not tested

[a] – Primary enzymes responsible for metabolism of the respective NME

[b] – Results are based on published literature presented in the NDA review package

[c] – Eluxadoline was not metabolized based on in vitro studies, but metabolism could not be ruled out according to the sponsor; more in vitro evaluations for eluxadoline as a substrate were requested as a PMR

[d] – Only P-gp and BCRP were tested

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Table 3. Enzymes inhibition interactions, in vitro to in vivo translation

Perpetrator	IC_{50} (μM)	R_1 or R_2	AUC Ratio	C_{max} Ratio	In Vivo Victim	Reference
Alectinib	2.0 (K_i, competitive) (CYP2C8)	1.6 [a]	1.08 [b]	1.06 [b]	Repaglinide	(FDA, 2015b)
	$K_I \geq 60$, K_{inact} = 0.0624 /min (CYP3A4)	N/A	0.97	0.92	Midazolam	
Alectinib Metabolite M4	K_I = 369, K_{inact} = 0.0620 /min (CYP3A4)	N/A				
Brexpiprazole	8.19 (CYP2B6, bupropion), 5.01 (K_i, inhibition type N/P), no TDI observed	1.092	1.02	0.96	Bupropion	(FDA, 2015p)
	22.23 (CYP2C9, diclofenac), no TDI observed	1.041	N/T			
	39.82 (CYP2C19, (S)-mephenytoin), no TDI observed	1.023	N/T			
	13.44 (CYP2D6, bufuralol), no TDI observed	1.068 [c]	0.96		Dextromethorphan	
	29.88, K_I = 32.1, K_{inact} = 0.02 /min, K_{obs} = 0.00024 /min (CYP3A, midazolam)	R_2 = 4.0 [a,d] with k_{deg} = 0.00008 /min	1.10	0.96	Lovastatin	

	40.78, K_I = 4.7, K_{inact} = 0.022 /min, K_{obs} = 0.00169 /min (CYP3A, testosterone)	R_2 = 22.1[a, e] with k_{deg} = 0.00008 /min		
Cangrelor Metabolite AR-C69712	58-59 (CYP2C19)	< 1.1	N/T	(FDA, 2015ab)
Cangrelor Metabolite AR-C90439	58-59 (CYP2C19)	< 1.1	N/T	
Cariprazine[f]	Weak (value N/P, CYP1A2)	N/A		(FDA, 2015v)
	weak (value N/P, CYP2A6)	N/A		
	weak (value N/P, CYP2C9)	N/A		
	weak (value N/P, CYP2C19)	N/A		
	weak (value N/P, CYP2D6)	N/A		
	weak (value N/P, CYP2E1)	N/A		
	weak (value N/P, CYP3A4)	N/A		
Cariprazine Metabolites DCAR	Weak (value N/P, CYP1A2)	N/A		
	weak (value N/P, CYP2C9)	N/A		
	weak (value N/P,	N/A		

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	CYP2D6)		
	weak (value N/P, CYP3A4)	N/A	
Cariprazine Metabolites DDCAR	Weak (value N/P, CYP1A2)	N/A	
	Weak (value N/P, CYP2C9)	N/A	
	weak (value N/P, CYP2D6)	N/A	
	weak (value N/P, CYP3A4)	N/A	
Cholic acid	38.1% ($P < 0.01$) at 100 µM (UGT1A1, 4-methylumbelliferone)	N/A	(Fang et al., 2013; FDA, 2015e)
	13.9% ($P < 0.05$) at 100 µM (UGT1A8, 4-methylumbelliferone)	N/A	
	25.65% ($P < 0.01$) at 100 µM (UGT1A10, 4-methylumbelliferone)	N/A	
	27.9% ($P < 0.01$) at 100 µM (UGT2B15, 4-	N/A	

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	methylumbelliferone)					
Cobimetinib	1.8, 1.1 (unbound K_i) (CYP2D6, bufuralol) 5.9 (CYP3A, testosterone); 17, 7.6 (unbound K_i) (CYP3A, midazolam), TDI (value N/P)	1.5 [a]	0.65	0.92	Dextromethorphan	(FDA, 2015z)
		1.2 [a] (testosterone), 1.1 [a] (midazolam)	1.02	1.05	Midazolam	
Daclatasvir	11.0 (CYP3A4, testosterone), 31.8 (CYP3A4, midazolam), no TDI observed	1.42 [a,g] (testosterone), 1.15 [a,g] (midazolam)	0.85	0.94	Midazolam	(FDA, 2015h)
Eluxadoline	20 (CYP2E1, chlorzoxazone) -5% (coincubation) and 42% (pre-incubation) at 50 µM (CYP3A4/5, midazolam) 1% (coincubation) and 30-40% (pre-incubation) at 50 µM (CYP3A4/5, testosterone)	1.00 [g]	N/T			(FDA, 2015u)
		N/A	1.05	0.98	Ethinyl estradiol	
		N/A	1.06	1.05	Norethindrone	
Flibanserin	6.4 (K_i) (CYP2B6)	1.17 [a,g]	1.03	1.03	Bupropion	(FDA, 2015a)
	7.5 (K_i) (CYP3A4)	1.14 [a,g]	1.31, simvastatin	1.15, simvastatin	Simvastatin	

			acid 1.47	acid 1.36		
Isavuconazonium sulfate Metabolite isavuconazole	2.86 (K_i) (CYP2C8)	6.98 [a,g]	No effect [h] (value N/P)	No effect [h] (value N/P)	Repaglinide	(FDA, 2015g)
	4.78 (K_i) (CYP2C9)	4.58 [a,g]	No effect [h] (value N/P)	No effect [h] (value N/P)	(S)-warfarin	
	5.40 (K_i) (CYP2C19)	4.17 [a,g]	No effect [h] (value N/P)	No effect [h] (value N/P)	Omeprazole	
	4.82 (K_i) (CYP2D6)	4.55 [a,g]	No effect [h] (value N/P)	No effect [h] (value N/P)	Dextromethorphan	
	0.622-1.93 (K_i) (CYP3A4)	9.86-28.49 [a,g]	2.03	1.72	Midazolam	
Ivabradine	46 (CYP3A4, midazolam)	1.00 [g]	N/T			(FDA, 2015f)
	17 (CYP3A5, midazolam)	1.01 [g]	N/T			
	140 (K_i) (CYP3A4, midazolam)	1.00 [g]	N/T			
Ivabradine Metabolite S18982	Weak inhibition (value N/P, CYP3A4/5, testosterone)	N/A	N/T			
Lenvatinib	10.1 (CYP2C8, paclitaxel)	1.20-1.31 [a,g]	1.01 [b]	1.00 [b]	Repaglinide	(FDA, 2015m)
	K_I = 72.266, K_{inact} = 5.01 /h (CYP3A, midazolam)	N/P	1.24 [b]	1.21 [b]	Midazolam	
	10.6 (UGT1A1, estradiol)	1.19-1.29 [g]	N/T			

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	14.0 (UGT1A4, trifluoperazine)	1.14-1.22 [g]	N/T			
Lesinurad	16.2 (CYP2C8)	1.00 [g]	1.31	1.27	Repaglinide	(FDA, 2015ag)
	40.7 (CYP2C9)	1.00 [g]	1.04	1.03	(S)-warfarin	
		1.00 [g]	1.11	1.06	Tolbutamide	
	148 (UGT1A1)	1.00 [g]	N/T			
	384 (UGT2B7)	1.00 [g]	N/T			
Lumacaftor	Value N/P (CYP2C8)	N/A				(FDA, 2015ad)
	value N/P (CYP2C9)	N/A				
Osimertinib	22.8 (CYP2C8)	< 1.1				(FDA, 2015ae)
	5.1 (CYP3A)	> 1.1 [a]	PMR			
Palbociclib	K_I = 10, K_{inact} = 0.036 /min (CYP3A, midazolam)	R_2 = 1.05 with k_{deg} = 0.18 /min	1.58	1.38	Midazolam	(FDA, 2015k)
	K_I = 19, K_{inact} = 0.087 /min (CYP3A, testosterone)	R_2 = 1.06 with k_{deg} = 0.18 /min				
Palbociclib Metabolite M17	16 (CYP3A, felodipine)	< 1.1	N/T			
	K_I = 7.0, K_{inact} = 0.094 /min (CYP3A, midazolam)	1.01	N/T			
	K_I = 6.4, K_{inact} = 0.15 /min (CYP3A, testosterone)	1.03	N/T			
Panobinostat	15-75 (CYP2C19), no TDI observed	< 1.1	N/T			(FDA, 2015j)

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	2, 0.167 (K_i) (CYP2D6), no TDI observed;	1.37 [a]	1.20-2.30	1.20-3.00	Dextromethorphan	
	15-75, K_I = 12, K_{inact} = 0.137 /h (CYP3A4/5)	R2 = 1.4 [a] with k_{deg} = 0.000321 /min, K_{obs} = 0.000117 /min	1.04 [b]	1.04 [b]	Midazolam	
Rolapitant	39% at 100 µM (coincubation), 90 (preincubation) (CYP1A2, phenacetin)	N/A	N/T			(FDA, 2015s)
	22 (coincubation), 10 (preincubation) (CYP2A6, coumarin)	N/A	N/T			
	13 (CYP2B6, bupropion), no TDI observed	1.13 [a]	1.32	1.09	Efavirenz	
	23 (CYP2C8, amodiaquine), no TDI observed	< 1.1	1.27	1.26	Repaglinide	
	9.6 (CYP2C9, diclofenac), no TDI observed	1.18 [a]	1.05	0.96	Tolbutamide	
	8.7 (CYP2C19, (S)-mephenytoin), no TDI observed	1.20 [a]	1.34	1.48	Omeprazole	
	7.1, 3.4 (Ki, competitive)	1.50 [a]	3.33	2.77	Dextromethorphan	

	(CYP2D6, dextromethorphan), no TDI observed					
	49 (coincubation), 35 (preincubation) (CYP3A4/5, testosterone)	< 1.1	0.97	0.87	Midazolam	
	41 (coincubation), 28 (preincubation) (CYP3A4/5, midazolam)	< 1.1				
Rolapitant Metabolite M19	8.65 (CYP2B6, bupropion)	N/A				
	21.1% at 10 µM (CYP2C9, diclofenac)	N/A				
	44.8% at 10 µM (CYP2C19, (S)-mephenytoin)	N/A				
	31.4% at 10 µM (CYP2D6, dextromethorphan)	N/A				
Sacubitril[i]	15 (CYP2C8)	N/A	N/T			(FDA, 2015i)
	20 (CYP2C19)	N/A	No effect (value N/P)	No effect (value N/P)	Omeprazole	
Sacubitril Metabolite	40 (CYP2C9)	N/A	No effect (value N/P)	No effect (value N/P)	(S)-warfarin	

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			No effect (value N/P)	No effect (value N/P)	Carvedilol	
Selexipag	3.6 (CYP2C8), no TDI observed	1.02 [g]	N/T			(FDA, 2015af)
	8.3 (CYP2C9), no TDI observed	1.00 [g]	1.00	1.00	(S)-warfarin	
Selexipag Metabolite ACT-333679	15 (CYP2C8), no TDI observed	N/A				
	32 (CYP2C9), no TDI observed	N/A				
Sonidegib	0.045 (K_i, inhibition type N/P) (CYP2B6),	34 [a]	N/T [j]			(FDA, 2015o)
	1.7 (K_i, inhibition type N/P) (CYP2C9), no TDI observed	1.8 [a]	N/T [j]			
Tenofovir alafenamide fumarate	7.4 (CYP3A, testosterone), 7.6 (CYP3A, midazolam), no TDI observed	1.00 [g]	N/T			(FDA, 2015aa)
Uridine triacetate	6600 (CYP2C19)	1.00 [g]	N/T			(FDA, 2015w)
	8300 (CYP3A)	1.00 [g]	N/T			
Uridine triacetate Metabolite uridine	5100 (CYP2C19)	N/A				
	2000 (CYP3A)	N/A				

N/A – not applicable; N/P – not provided; N/T – not tested; PMR – study has been requested as a PMR; the inhibition studies were performed using HLMs except cholic acid and ivabradine, for which the inhibition studies were performed using

recombinant enzymes; if in vitro substrate not provided, then not listed in the table; either CYP3A or CYP3A4 depending on how the enzyme is presented in the NDA reviews.

[a] – Values exceed the FDA cut-off value of 1.1

[b] – Results are obtained from PBPK modeling and simulations

[c] – The ratio is dextromethorphan/dextrorphan urinary ratio with or without brexpiprazole

[d] – R_2 = 1.5 assuming k_{deg} of 0.0005 /min

[e] – R_2 = 4.4 assuming k_{deg} of 0.0005 /min

[f] –The in vitro evaluation of inhibition potential of cariprazine toward CYP2C8 as well as DCAR and DDCAR toward CYP2B6, 2C8, and 2C19 has been requested as a PMR

[g] – R_1 value was calculated by the DIDB Editorial Team using K_i or assuming $K_i = IC_{50}/2$

[h] – Prodrug isavuconazonium sulfate was administered in the clinical studies

[i] – Perpetrator was administered as the combination drug

[j] – Clinical studies are undergoing

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Table 4. Enzymes induction interactions, in vitro to in vivo translation

Perpetrator	Induction Effect	C_{max} (µM)	AUC Ratio	C_{max} Ratio	In Vivo Victim	Reference
Alectinib[a]	2.1-fold in mRNA at 1 µM (CYP2B6)	1.38				(FDA, 2015b)
	2.1-fold in mRNA at 1 µM (CYP3A4[b])		0.97	0.92	Midazolam	
Cangrelor	Induction observed at 100 µM, value N/P (significantly lower than positive control) (CYP2C9)	0.77	N/T			(FDA, 2015ab)
	induction observed at 100 µM, value N/P (significantly lower than positive control) (CYP3A4/5)					
Cangrelor Metabolite AR-C69712	Induction observed at 100 µM, value N/P (significantly lower than positive control) (CYP2C9)					
	Induction					

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	observed at 100 µM, value N/P (significantly lower than positive control) (CYP3A4) 0.4-fold (P < 0.001) in mRNA at 50 µM (CYP3A4) 9.1-fold at 10 µM in mRNA (but not activity, also no PXR activation up to 25 µM) at 10 µM (CYP3A4[b])					
Cholic acid		1.88	N/T			(FDA, 2015e; Zhang et al., 2015)
Cobimetinib		0.51	1.02	1.06	Midazolam	(FDA, 2015z)
Daclatasvir	0.458- to 1.36-fold with 0.5-fold observed in two lots at 9.6 µg/mL (CYP1A2) 1.66- to 3.95-fold in mRNA at 9.6 µg/mL (CYP2B6) 8.76- to 27.3-fold in mRNA at 9.6 µg/mL (CYP3A4[b])	2.34	N/T			(FDA, 2015h)
			N/T			
			0.85	0.94	Midazolam	
Deoxycholic acid	43% of positive control in activity at 10 µM in one	2.61	N/T			(FDA, 2015l)

	out three lots (CYP1A2) 2.77-fold (≤ 10% of positive control) in activity (concentrations N/P) (CYP1A2) 13.4-fold (84.3% of positive control) in activity (concentrations N/P) (CYP2B6) 2.63-fold (37.4% of positive control) in activity (concentrations N/P) (CYP2C8[b]) 3.43-fold (42.2% of positive control) in activity (concentrations N/P) (CYP3A4/5[b])					
Isavuconazonium sulfate metabolite isavuconazole		17.14	No effect (value N/P)	No effect (value N/P)	Caffeine	(FDA, 2015g)
			0.58	0.69	Bupropion	
			No effect (value N/P)	No effect (value N/P)	Repaglinide	
			0.69	N/P	Ritonavir	
			0.73	N/P	Lopinavir	
			No effect (value N/P)	No effect (value N/P)	Ethinyl estradiol	
			No effect (value N/P)	No effect (value N/P)	Norethindrone	
			No effect (value N/P)	No effect (value N/P)	Prednisone	
Lenvatinib	1.65-fold in	1.01-1.55	1.24 (NS,	1.21 (NS,	Midazolam	(FDA, 2015m)

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	mRNA and 1.54-fold in activity up to 3 µM (CYP3A4[b]) 3.04-fold in mRNA and 3.15-fold in activity at 30 µM (CYP2B6) 4.18-fold in mRNA at 30 µM and 2.38-fold in activity at 10 µM (CYP2C8[b]) 3.46-fold in mRNA at 30 µM and 1.04-fold in activity at 10 µM (CYP2C9[b]) 1.36-fold in mRNA at 100 µM and 3.25-fold in activity at 30 µM (CYP2C19) 3-fold and 67% of positive control rifampin in activity (mRNA not evaluated) at 10 µM (CYP3A4/5)		PBPK)	PBPK)		
Lesinurad		0.000015	N/T			(FDA, 2015ag)
			1.10	0.99	Repaglinide	
			1.04	1.03	(S)-warfarin	
			1.06	1.11	Tolbutamide	
			N/T			
			0.58	0.61	Amlodipine	

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			0.66	0.66	Sildenafil	
			0.73	0.99	Atorvastatin	
			0.75	0.82	Colchicine	
Lumacaftor	Induction observed, value N/P (CYP2B6)	55.26	N/T			(FDA, 2015ad)
	induction observed, value N/P (CYP2C8[b])		N/T			
	induction observed, value N/P (CYP2C9[b])		N/T			
	induction observed, value N/P (CYP2C19)		N/T			
	Induction observed, value N/P (CYP3A4/5)		0.20	N/P	Ivacaftor	
Osimertinib	16% of positive control in activity at 3.3 µM (CYP1A2)	0.13	N/T			(FDA, 2015ae)
	45% of positive control in activity at 3.3 µM		N/T			

	(CYP3A4/5[b]) activation of PXR (value N/P) 18.1-fold and 80% of positive control in activity at 10 µM (CYP1A2[b]) 2.10-fold (P < 0.05) in activity at 10 µM (CYP2C8[b]) 1.16-fold (P < 0.05) in activity at 10 µM (CYP2C9[b]) 2.42-fold (P < 0.05) in activity at 10 µM (CYP2C19[b]) 3.03-fold (P < 0.05) and 68% of positive control in activity at 10 µM (CYP3A4/5[b]) 38% of positive control rifampin in mRNA at 10 µM (CYP3A4) 26% of positive control rifampin in mRNA at 10					
Rolapitant		1.93	N/T			(FDA, 2015s)
			1.27	1.26	Repaglinide	
			1.02	1.00	Tolbutamide	
			1.34	1.48	Omeprazole	
			0.97	0.87	Midazolam	
Selexipag		0.032	N/T			(FDA, 2015af)
Selexipag Metabolite ACT-333679						

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	µM (CYP3A4)		
Tenofovir alafenamide fumarate	3.89-fold activation of PXR and 31% of positive control at 50 µM (no induction of CYP3A though)	0.00033	(FDA, 2015aa)

N/P – not provided; N/T – not tested; R_3 values were not provided for any of the compounds listed; induction experiments were conducted using human hepatocytes; either CYP3A or CYP3A4 depending on how the enzyme is presented in the NDA reviews.

[a] – Metabolite M4 was formed in human hepatocytes; therefore, it may also be responsible for the observed induction effect

[b] – Inhibition of the same enzyme was also observed

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Table 5. Hepatic OATP inhibition interactions, in vitro to in vivo translation

Perpetrator	OATP	In vitro substrate	IC_{50} (µM)	C_{max} / IC_{50}	AUC Ratio	C_{max} Ratio	In Vivo Victim	Reference
Brexpiprazole	1B1	Estradiol 17-β-glucuronide	8.39	0.05			N/T	(FDA, 2015p)
Brexpiprazole metabolite DM-3411	1B1	Estradiol 17-β-glucuronide	9.13	0.01			N/T	
Cobimetinib	1B1	Estrone-3-sulfate	118	< 0.1			N/T	(FDA, 2015z)
	1B3	Fluo-3	85	< 0.1			N/T	
Daclatasvir	1B1	BMS-791553	2.3	1.02[a, b]	1.47	1.84	Rosuvastatin	(FDA, 2015h)
	1B3	Cholecystokinin octapeptide	5.7	0.41[a, b]				
Deoxycholic acid	1B1	N/P	N/P	0.14[b]			N/T, R < 1.25	(FDA, 2015l)
	1B3	N/P	N/P	0.11[b]			N/T, R < 1.25	
Edoxaban	1B1	N/P	62.7	0.01[a]			N/T	(FDA, 2015q)
	1B3	N/P	50.8	0.01[a]			N/T	
Eluxadoline	1B1	Estradiol 17-β-glucuronide	32.6% at 400 ng/mL	N/A	1.41	1.18	Rosuvastatin	(FDA, 2015u)
Isavuconazonium sulfate	1B1	N/P	11.2	1.53[a, b]	1.40	1.05	Atorvastatin	(FDA, 2015g)
Lenvatinib	1B1	Estradiol 17-β-glucuronide	7.29	0.21[a, b]			N/T	(FDA, 2015m)
Lesinurad	1B1	N/P	9.3	1.8[b]	1.01	1.17	Atorvastatin	(FDA, 2015ag)
	1B3	N/P	43.1	0.4[b]				

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Osimertinib	1B1	N/P	22	0.05			N/T	(FDA, 2015ae)
	1B3	N/P	52.5	0.02			N/T	
Panobinostat	1B1	N/P	N/P				N/T, R = 1	(FDA, 2015j)
Sacubitril	1B1	N/P	1.9	3.11[b]	1.30	1.75	Atorvastatin	(FDA, 2015i)
	1B3	N/P	3.8	1.55[a, b]				
Sacubitril metabolite LBQ657	1B1	N/P	126	N/A				
Selexipag	1B1	Atorvastatin	2.4	0.01[a]			N/T	(FDA, 2015af)
	1B3	Taurocholic acid	1.7	0.02[a]			N/T	
Selexipag metabolite ACT-333679	1B1	Atorvastatin	3.5	N/A			N/T	
	1B3	Taurocholic acid	4.1	N/A			N/T	
Tenofovir alafenamide fumarate	1B1	Fluo-3	29.8% at 100 µM	N/A				(FDA, 2015aa)
	1B3	Fluo-3	25.5% at 100 µM	N/A				

N/A – not applicable; N/P – not provided; N/T - not tested.

[a] – Ratio was calculated by the DIDB Editorial Team

[b] – Values exceed the FDA cut-off value of 0.1

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Table 6. BCRP inhibition interactions, in vitro to in vivo translation

Perpetrator	In vitro substrate	IC_{50} (μM)	$[I]_1/ IC_{50}$	$[I]_2/ IC_{50}$	AUC Ratio	C_{max} Ratio	In Vivo Victim	Reference
Alectinib	N/P	0.1	13[a, b]	49729[a, b]			N/T[d]	(FDA, 2015b)
Alectinib metabolite M4	N/P	2.6	0.2	N/A				
Brexpiprazole	Prazosin	1.16	0.40[a, b]	32[a, b]	1.12		Rosuvastatin	(FDA, 2015p)
Brexpiprazole metabolite DM-3411	Prazosin	3.04	0.047	N/A				
Cariprazine	N/P	Weak (value N/P)					N/T	(FDA, 2015v)
Cobimetinib	Estrone-3-sulfate	3.3	0.16[a]	137[a, b]			N/T	(FDA, 2015z)
Daclatasvir	Genistein	10.9	0.21[a, b]	30[a, b]	1.47	1.84	Rosuvastatin	(FDA, 2015h)
Isavuconazonium sulfate	N/P	92	0.19[a, b]	20[a, b]	No effect (value N/P)		Methotrexate	(FDA, 2015g)
Lesinurad	Methotrexate	62.7% at 100 μM	< 0.01				N/T	(FDA, 2015ag)
Osimertinib	N/P	2	0.063[a]	320[b]			N/T, PMR	(FDA, 2015ae)
Rolapitant	Cladribine	0.172	10[b]	8364[a, b]	2.18	2.38	Sulfasalazine	(FDA, 2015s)
Selexipag	Methotrexate	1.9	0.017[a]	0.42[a]			N/T	(FDA, 2015af)
Selexipag metabolite ACT-333679	Methotrexate	5.6	N/A	N/A				
Sonidegib	N/P	1.5	0.98[a, b]	783[a, b]			N/T	(FDA, 2015o)

N/P – not provided; N/T - not tested; PMR – study has been requested as a PMR.

[a] – Ratio was calculated by the DIDB Editorial Team

[b] – Values exceed the FDA cut-off value of 0.1 ($[I]_1$/ IC_{50}) or 10 ($[I]_2/IC_{50}$)

[c] – A clinical study was recommended in the comments by FDA reviewers

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Table 7. P-gp inhibition interactions, in vitro to in vivo translation

Perpetrator	In vitro substrate	IC_{50} (μM)	$[I]_1/ IC_{50}$	$[I]_2/ IC_{50}$	AUC Ratio	C_{max} Ratio	In Vivo Victim	Reference
Alectinib	N/P	1.1	1.2[a, b]	4521[a, b]			N/T[d]	(FDA, 2015b)
Alectinib metabolite M4	N/P	4.7	0.1	N/A				
Brexpiprazole	Digoxin	6.31	0.07[a]	5.85[a]	1.04		Fexofenadine	(FDA, 2015p)
Brexpiprazole metabolite DM-3411	Digoxin	7.84	0.018	N/A				
Cariprazine	N/P	Weak (value N/P)	N/A				N/T	(FDA, 2015v)
Cariprazine metabolite DCAR	N/P	Weak (value N/P)	N/A					
Cariprazine metabolite DDCAR	N/P	Weak (value N/P)	N/A					
Daclatasvir	Digoxin	4.4	0.53[a, b]	74[a, b]	1.27	1.65	Digoxin	(FDA, 2015h)
Edoxaban	N/P	No inhibition	N/A		No effect (value N/P)		Digoxin	(FDA, 2015q)
Flibanserin	Digoxin	Weak (value N/P)	N/A		1.93	1.46	Digoxin	(FDA, 2015a)
Isavuconazonium sulfate	N/P	25.7	0.67[a, b]	71[a, b]	1.25	1.33	Digoxin	(FDA, 2015g)
Ivabradine	N/P	No inhibitio			No effect		Digoxin	(FDA, 2015f)

		n			(value N/P)			
Ivabradine metabolite S18982	N/P	5.3	≤ 0.1	N/A				
Lesinurad	N/P	1000	0.02	1.98[a]			N/T	(FDA, 2015ag)
Rolapitant	Digoxin	7.36	0.23[a, b]	196[a, b]	1.27	1.67	Digoxin	(FDA, 2015s)
Sacubitril	Rhodamine 123	No inhibition			No effect (value N/P)		Digoxin	(FDA, 2015i)
Uridine triacetate	Digoxin	344	N/A[d]	108[a, b]			N/T	(FDA, 2015w)

N/A – not applicable; N/P – not provided; N/T - not tested.

[a] – Ratio was calculated by the DIDB Editorial Team

[b] – Values exceed the FDA cut-off value of 0.1 ($[I]_1/IC_{50}$) or 10 ($[I]_2/IC_{50}$)

[c] – A clinical study was recommended in the comments by FDA reviewers

[d] – Uridine triacetate is rapidly converted to uridine, and therefore has a low systemic circulation; uridine did not inhibit P-gp in vitro

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Table 8. Clinically significant inhibitions, NMEs as victims or perpetrators

Victim Drug (Dose)	Inhibitor (Dose)	Enzymes / Transporters Possibly Involved	AUC Ratio	C_{max} Ratio	Study Design / Population[a]	Labeling Impact	Reference
DDIs with AUC ratio ≥ 2 for victim exposure							
Ivabradine[b]	Josamycin	CYP3A4	7.70	3.60	N/P	Contraindication with strong CYP3A4 inhibitors	(FDA, 2015f)
Ivabradine[b]	Ketoconazole (200 mg once daily)	CYP3A4, P-gp	7.70	3.60	N/P	Contraindication with strong CYP3A4 inhibitors	(FDA, 2015f)
Cobimetinib (10 mg SD)[b]	Itraconazole (200 mg once daily 14 days)	CYP3A4, P-gp	6.62	3.17	One-sequence / 15 healthy subjects	Avoid CYP3A strong inhibitors	(FDA, 2015z)
Flibanserin (100 mg SD)[b]	Fluconazole (200 mg once daily 6 days)	CYP3A4, CYP2C19 (minor)	6.41	2.11	One-sequence / 15 healthy females	Contraindication with CYP3A4 moderate inhibitors	(FDA, 2015a)
Isavuconazonium sulfate (200 mg SD)[b,c]	Ketoconazole (200 mg twice daily 24 days)	CYP3A	5.22	1.09	N/P	Contraindication with strong CYP3A4 inhibitors	(FDA, 2015g)
Flibanserin (50 mg SD)[b]	Ketoconazole (400 mg once daily 5 days)	CYP3A4, CYP2C8/9 (minimal)	4.61	1.84	Random Crossover / 20 healthy females	Contraindication with CYP3A4 strong inhibitors	(FDA, 2015a)
Cobimetinib (60	Erythromyci	CYP3A4,	4.27	3.76	PBPK	Avoid CYP3A	(FDA,

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mg once daily 35 days)[b]	n (500 mg three times daily 35 days)	P-gp	(PBPK)	(PBPK)	modeling/simulations of healthy subjects	moderate inhibitors	2015z)
Eluxadoline (100 mg SD)[b]	Cyclosporine (600 mg SD)	OATP1B1, MRP2 (minimal)	4.20	6.81	Random Crossover / 30 healthy subjects	Reduce dose with OATP1B1 inhibitors; monitor for adverse reactions	(FDA, 2015u)
Cariprazine (0.5 mg once daily 14 days)[b]	Ketoconazole (400 mg)	CYP3A4	3.78	3.27	N/P /16 patients	Reduce dose with CYP3A strong inhibitors	(FDA, 2015v)
Dextromethorphan (30 mg SD)	Rolapitant (200 mg SD)[b]	CYP2D6	3.33	2.77	One-sequence / 26 subjects (CYP2D6 EMs and IMs)	Monitor for adverse reactions if concomitant use with other CYP2D6 substrates with a narrow therapeutic index cannot be avoided	(FDA, 2015s)
Cobimetinib (60 mg SD)[b]	Diltiazem (1200 mg twice daily)	CYP3A4, P-gp	3.26 (PBPK)	1.85 (PBPK)	PBPK modeling/simulations of healthy subjects	Avoid CYP3A moderate inhibitors	(FDA, 2015z)
Daclatasvir (10 mg SD)[b]	Ketoconazole (400 mg once daily 9 days)	CYP3A, CYP2C8 (minor), P-gp	3.01	1.57	One-sequence / 13 healthy subjects	Reduce dose with CYP3A strong inhibitors	(FDA, 2015h)
Ivabradine[b]	Diltiazem (1	CYP3A4, P-	3.00	2.50	N/P	Contraindication	(FDA,

	20 mg twice daily)	gp				with strong CYP3A4 inhibitors	2015f)
Dextromethorphan (60 mg SD)	Panobinostat (20 mg once daily 3 days)[b]	CYP2D6	2.30[d]	3.00[d]	One-sequence / 14 patients (CYP2D6 EMs)	Avoid CYP2D6 sensitive substrates or CYP2D6 substrates with a NTI	(FDA, 2015j)
Sonidegib (200 mg once daily at steady state)[b]	Erythromycin (500 mg once daily 120 days)	CYP3A	2.80 (PBPK)	2.40 (PBPK)	PBPK modeling/simulations of patients	Avoid long term use of CYP3A moderate inhibitors	(FDA, 2015o)
Rocuronium[e]	Sugammadex (4 mg/kg SD)[b, e]	not by CYPs	2.70	N/P	Parallel / 2	Adjust dose	(FDA, 2015y)
Tenofovir alafenamide fumarate (8 mg once daily 22 days)[b]	Cobicistat (150 mg once daily 10 days)	P-gp, BCRP, OATP1B1, OATP1B3	2.65	2.83	One-sequence / 12 healthy subjects	Combination drug	(FDA, 2015aa)
Flibanserin (50 mg SD)[b]	Itraconazole (200 mg once daily 7 days)	CYP3A4, CYP2C8/9 (minimal)	2.58	1.70	Random Crossover /12 healthy subjects	Contraindication with CYP3A4 strong inhibitors	(FDA, 2015a)
Sonidegib (800 mg SD)[b]	Ketoconazole (200 mg twice daily 14 days)	CYP3A	2.26	1.50	Parallel / 15 healthy subjects	Avoid CYP3A strong inhibitors	(FDA, 2015o)
Tacrolimus (5 mg SD)	Isavuconazonium	CYP3A4	2.25	1.42	N/P	Caution; adjust immunosuppressa	(FDA, 2015g)

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	sulfate[b]					nt's dose as needed	
Daclatasvir (60 mg once daily 7 days)[b]	Simepravir (150 mg once daily 7 days)	CYP3A, P-gp	2.20	1.60	Random Crossover / 15 healthy nonsmokers	Reduce dose when it is coadministered with simeprevir[f]	(FDA, 2015h)
Ivabradine[b]	Grapefruit juice	CYP3A4	2.20	1.60	N/P	Avoid concomitant use of moderate CYP3A4 inhibitors	(FDA, 2015f)
Sulfasalazine (500 mg SD)	Rolapitant (200 mg SD)[b]	BCRP	2.18	2.38	One-sequence / 20	Monitor for adverse events	(FDA, 2015s)
Brexpiprazole (2 mg SD)[b]	Ketoconazole (200 mg twice daily 7 days)	CYP3A4, CYP2D6	2.17	1.18	One-sequence / 12 healthy subjects (CYP2D6 EMs and IMs)	Reduce dose with CYP3A strong inhibitors	(FDA, 2015p)
Daclatasvir (60 mg once daily 4 days + 20 mg once daily 10 days)[b]	Atazanavir/ritonavir (300/100 mg once daily 10 days)	CYP3A	2.10	1.35	One-sequence / 14 healthy subjects	Reduce dose with CYP3A strong inhibitors	(FDA, 2015h)
Midazolam (3 mg SD)	Isavuconazonium sulfate[b]	CYP3A4	2.03	1.72	N/P	Caution; reduce dose	(FDA, 2015g)
Brexpiprazole (2 mg SD)[b]	Quinidine (324 mg once daily 7 days)	CYP3A4, CYP2D6	2.03 (EMs)	1.12 (EMs)	One-sequence / 11 healthy subjects (CYP2D6 EMs	Reduce dose with CYP2D6 strong inhibitors	(FDA, 2015p)

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					and IMs)		
Ivabradine[b]	Verapamil (120 mg twice daily)	CYP3A4, P-gp	2.00	1.90	N/P	Avoid concomitant use with moderate CYP3A4 inhibitors	(FDA, 2015f)
Selexipag[b]	Lopinavir and ritonavir	P-gp, OATP1B1, OATP1B3	2.00	2.00	N/P	None	(FDA, 2015af)
DDIs with 1.25 ≤ AUC ratio < 2 for victim exposure with dose recommendation							
Isavuconazonium sulfate[b,c]	lopinavir and ritonavir (400 mg/100 mg twice daily)	CYP3A	1.96	1.74	N/P	Caution with lopinavir/ritonavir, monitor for toxicity by isavuconazole	(FDA, 2015g)
Digoxin (0.5 mg SD)	Flibanserin (100 mg once daily 8 days)[b]	P-gp	1.93	1.46	Random Crossover / 23 healthy subjects	Increase monitoring of digoxin concentrations	(FDA, 2015a)
Edoxaban (60 mg SD)[b]	Ketoconazole (400 mg once daily 7 days)	P-gp	1.87	1.89	N/P / healthy subjects	Reduce dose with P-gp inhibitors	(FDA, 2015q)
Edoxaban (60 mg SD)[b]	Erythromycin (500 mg four times daily 8 days)	P-gp	1.85	1.68	N/P / healthy subjects	Reduce dose with P-gp inhibitors	(FDA, 2015q)
Palbociclib (125 mg SD)[b]	Itraconazole (200 mg once daily	CYP3A	1.85	1.35	One-sequence / 11 healthy subjects	Avoid CYP3A strong inhibitors	(FDA, 2015k)

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	11 days)						
Edoxaban (60 mg SD)[b]	Dronedarone (400 mg twice daily)	P-gp	1.84	1.45	N/P / healthy subjects	Reduce dose with P-gp inhibitors	(FDA, 2015q)
Sirolimus (2 mg SD)	Isavuconazonium sulfate[b]	CYP3A4	1.84	1.65	N/P	Caution; adjust immunosuppressant's dose as needed	(FDA, 2015g)
Edoxaban (60 mg SD)[b]	Quinidine (300 mg three times daily)	P-gp	1.75	1.75	N/P / healthy subjects	Reduce dose with P-gp inhibitors	(FDA, 2015q)
Edoxaban (60 mg SD)[b]	Cyclosporine (500 mg SD)	P-gp, OATP1B1 (metabolite M4)	1.73 (metabolite M4: 6.87)	1.74 (metabolite M4: 8.71)	N/P / healthy subjects	Reduce dose with P-gp inhibitors	(FDA, 2015q)
Trabectedin (1.3 mg/m2 SD (alone); 0.58 mg/m2 (coadministration))[b,e]	Ketoconazole (200 mg twice daily 15 doses)	CYP3A4, P-gp	1.69	1.21	Random Crossover / 8 patients	Avoid strong CYP3A inhibitors	(FDA, 2015x)
Midazolam (2 mg SD)	Palbociclib (125 mg once daily 8 days)[b]	CYP3A	1.58	1.38	Random Crossover / 26 healthy females	Reduce dose with sensitive CYP3A substrates with a NTI	(FDA, 2015k)
Lesinurad (400 mg SD)[b]	Fluconazole (400 mg loading dose + 200 mg once daily 2	CYP2C9	1.54	1.34	One-sequence / 12 healthy males	Caution with moderate CYP2C9 inhibitors	(FDA, 2015ag)

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	days)						
Simepravir (150 mg once daily 7 days)	Daclatasvir (60 mg once daily 7 days)[b]	CYP3A, OATP1B1, OATP1B3	1.51	1.43	Random Crossover / 24 healthy nonsmokers	Reduce dose when coadministered with simeprevir[f]	(FDA, 2015h)
Rosuvastatin (10 mg SD)	Daclatasvir (60 mg once daily 9 days)[b]	CYP3A, BCRP, OTATP1B1, OATP1B3	1.47	1.84	One-sequence / 21 healthy subjects	Monitor for adverse events	(FDA, 2015h)
Flibanserin (25-100 mg SD)[b]	Oral contraceptives	CYP3A4, CYP2C19 (minor)	1.42	1.12	N/P / 39 healthy female subjects and HSDD patients	Oral contraceptives and other weak CYP3A4 inhibitors may increases flibanserin exposures and incidence of adverse reactions	(FDA, 2015a)
Panobinostat (20 mg SD)[b]	Ketoconazole (400 mg once daily 5 days)	CYP3A, P-gp	1.66	1.62	One-sequence / 14 patients	Reduce dose with strong CYP3A inhibitors	(FDA, 2015j)
Panobinostat (25 mg 3 times a week for 3 weeks)[b]	Bortezomib (1.3 mg/m^2 twice a week for two weeks)[e]	CYP3A	1.42	1.50	One-sequence / 7 patients	Reduce dose with strong CYP3A inhibitors	(FDA, 2015j)
Rosuvastatin (20 mg SD)	Eluxadoline (100 mg SD)[b]	OATP1B1	1.41	1.18	Random Crossover / 27 healthy subjects	Reduce dose of rosuvastatin; caution for an	(FDA, 2015u)

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						increased risk of myopathy/rhabdomyolysis	
Atorvastatin (20 mg SD)	Isavuconazonium sulfate[b]	CYP3A4	1.40	1.05	N/P	Caution; monitor for adverse reactions	(FDA, 2015g)
Edoxaban (60 mg SD)[b]	Amiodarone (400 mg once daily 4 days)	P-gp	1.40	1.60	N/P	Reduce dose with P-gp inhibitors	(FDA, 2015q)
Mycophenylate mofetil (1 g SD)	Isavuconazonium sulfate (200 mg once daily)[b]	UGTs	1.35	0.89	N/P	Caution; monitor for toxicity	(FDA, 2015g)
Flibanserin (100 mg SD)[b]	Grapefruit juice (240 mL regular strength SD)	CYP3A4	1.34	1.07	One-sequence / 26 healthy females	Contraindication with CYP3A4 moderate inhibitors	(FDA, 2015a)
Cyclosporine (300 mg SD)	Isavuconazonium sulfate[b]	CYP3A4	1.30	1.10	N/P	Caution; monitor cyclosporine concentrations and adjust dose as needed	(FDA, 2015g)
Edoxaban (60 mg once daily 5 days)[b]	Acetylsalicylic acid (325 mg once daily 5 days)	N/P	1.30	1.30	N/P / healthy volunteers	Monitor for bleeding	(FDA, 2015q)
Digoxin (0.125 mg once daily 20 days)	Daclatasvir (60 mg once daily 10 days)[b]	P-gp	1.27	1.65	One-sequence / 15 healthy subjects	monitor digoxin concentrations; adjust digoxin doses if necessary	(FDA, 2015h)

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Digoxin (0.5 mg SD)	Rolapitant (180 mg SD)[b]	P-gp	1.27	1.67	One-sequence / 16	Monitor for adverse reactions for concomitant use of P-gp substrates with an NTI	(FDA, 2015s)
Digoxin (0.5 mg SD)	Isavuconazonium sulfate (200 mg once daily)[b]	P-gp	1.25	1.33	N/P	Adjust dose for P-gp substrates with an NTI; monitor serum digoxin concentrations	(FDA, 2015g)

N/P – not provided; SD, single dose

[a] – The number of subjects listed represents the number of subjects who completed both treatments, as described in the DIDB

[b] – 2015 NMEs

[c] – Isavuconazonazole was measured

[d] – Large variabilities were observed; maximum values are obtained from the product label

[e] – Drug was given intravenously

[f] – Labeling recommendations are extracted from the Clinical Pharmacology and Biopharmaceutics Review(s)

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Table 9. Clinically significant inductions

Victim Drug (Dose)	Inducer (Dose)	Main Enzymes /Transporters Possibly Involved	AUC Ratio	C_{max} Ratio	Study Design / Population[a]	Labeling Impact	Reference
DDIs with AUC ratio ≤ 0.5 for victim exposure							
Isavuconazonium sulfate[b]	Rifampin (600 mg once daily)	CYP3A	0.03	0.25	N/P	Contraindication with strong CYP3A4 inducers	(FDA, 2015g)
Flibanserin (100 mg SD)[b]	Rifampin (600 mg once daily 9 days)	CYP3A4, CYP2C19 (minor)	0.04	0.10	Random Crossover / 23 healthy females	CYP3A4 inducers not recommended	(FDA, 2015a)
Rolapitant (200 mg SD)[b]	Rifampin (600 mg once daily 14 days)	CYP3A4	0.12	0.68	One-sequence / 20 healthy subjects	Avoid CYP3A strong inducers	(FDA, 2015s)
Palbociclib (125 mg SD)[b]	Rifampin (600 mg once daily 12 days)	CYP3A	0.15	0.28	One-sequence / 14 healthy subjects	Avoid moderate and strong CYP3A inducers	(FDA, 2015k)
Cobimetinib (60 mg SD)[b]	Rifampin (600 mg once daily)	CYP3A4, P-gp	0.17 (PBPK)	0.37 (PBPK)	PBPK modeling/simulations of healthy subjects	Avoid CYP3A strong inducers	(FDA, 2015z)
Ivacaftor	Lumacaftor[b]	CYP3A	0.20	N/P	N/P	Coadministration with strong CYP3A inducers is not recommended	(FDA, 2015ad)
Daclatasvir (60	Rifampin (600	CYP3A,	0.21	0.44	One-sequence / 14	Contraindicatio	(FDA,

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mg SD)[b]	mg once daily 9 days)	CYP2C8 (minor), P-gp			healthy Asian Males	n with strong CYP3A inducers	2015h)
Brexpiprazole (4 mg SD)[b]	Rifampin (600 mg once daily 13 days)	CYP3A4	0.24	0.69	One-sequence / 16 healthy subjects	Increase dose with CYP3A strong inducers	(FDA, 2015p)
Ixazomib citrate (4 mg SD)[b]	Rifampin (600 mg once daily 14 days)	CYP3A	0.26	0.46	Parallel / 16 patients	Avoid CYP3A strong inducers	(FDA, 2015ac)
Cobimetinib (60 mg once daily 21 days)[b]	Efavirenz (600 mg once daily 21 days)	CYP3A4, P-gp	0.27 (PBPK)	0.29 (PBPK)	PBPK modeling/ simulations of healthy subjects	Avoid CYP3A moderate inducers	(FDA, 2015z)
Alectinib (600 mg SD)[b]	Rifampin (600 mg once daily 13 days)	CYP3A	0.27	0.49	One-sequence / 24 healthy subjects	None	(FDA, 2015b)
Sonidegib (800 mg SD)[b]	Rifampin (600 mg once daily 14 days)	CYP3A	0.28	0.46	Parallel / 16 healthy subjects	Avoid CYP3A strong inducers	(FDA, 2015o)
Sonidegib (200 mg once daily at steady state)[b]	Efavirenz (600 mg once daily 120 days)	CYP3A	0.31 (PBPK)	0.4 (PBPK)	PBPK modeling/ simulations of patients	Avoid CYP3A moderate inducers	(FDA, 2015o)
Panobinostat (20 mg SD)[b]	Rifampin (600 mg once daily 14 days)	CYP3A, P-gp	0.35 (PBPK)	0.43 (PBPK)	PBPK modeling/ simulations of 10 trials of 10 healthy subjects	Avoid CYP3A strong inducers	(FDA, 2015j)
Ivabradine[b]	St. John's Wort extract	CYP3A4, P-gp	0.40	0.50	N/P	Avoid concomitant use of CYP3A4 inducers	(FDA, 2015f)

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DDIs with 0.8 < AUC ratio ≤ 0.5 for victim exposure with dose recommendation

Trabectedin (1.3 mg/m^2 SD)[b,c]	Rifampin (600 mg once daily 6 days)	CYP3A4, P-gp	0.55	0.77	Random Crossover/ 8 patients	Avoid CYP3A strong inducers	(FDA, 2015x)
Amlodipine (5 mg once daily 28 days)	Lesinurad (400 mg once daily 24 days)[b]	CYP3A	0.58	0.61	One-sequence / 13 healthy males	Monitor for a potential reduction in efficacy of sensitive CYP3A substrates	(FDA, 2015ag)
Bupropion	Isavuconazonium sulfate (200 mg once daily)[b]	CYP2B6	0.58	0.69	N/P	Caution	(FDA, 2015g)
Edoxaban (60 mg SD)[b]	Rifampin (600 mg once daily 7 days)	P-gp	0.60	1.00	N/P	Avoid	(FDA, 2015q)
Lesinurad (400 mg SD)[b]	Rifampin (600 mg once daily 14 days)	CYP2C9	0.62	0.76	One-sequence / 14 healthy males	Monitor for potential reduction in efficacy during concomitant use with moderate CYP2C9 inducer	(FDA, 2015ag)
Sildenafil (50 mg SD)	Lesinurad and allopurinol (300 mg/ 200 mg once daily 10 days)[b]	CYP3A	0.66	0.66	Random Crossover / 12 healthy males	Monitor for a potential reduction in efficacy of sensitive	(FDA, 2015ag)

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						CYP3A substrates	
Daclatasvir (60 mg once daily 14 days and 120 mg once daily 5 days)[b]	Efavirenz (600 mg once daily 14 days)	CYP3A, P-gp	0.68	0.83	One-sequence / 17 healthy subjects	Increase dose with CYP3A moderate inducers	(FDA, 2015h)
Ritonavir (100 mg twice daily)	Isavuconazonium sulfate[b]	CYP3A	0.69	Not provided	N/P	Caution	(FDA, 2015g)
Lopinavir (400 mg twice daily)	Isavuconazonium sulfate[b]	CYP3A	0.73	Not provided	N/P	Caution	(FDA, 2015g)
Flibanserin (100 mg SD)[b]	Etravirine (200 mg twice daily 15 days)	CYP3A4	0.75	0.97	One-sequence / 24 healthy females	CYP3A4 inducers not recommended	(FDA, 2015a)

N/P – not provided; SD, single dose

[a] – The number of subjects listed represents the number of subjects who completed both treatments, as described in the DIDB

[b] – 2015 NMEs

[c] – Drug was given intravenously

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Table 10. NMEs with HI-related labeling impact

Drug name	Max AUC Ratio	C_{max} Ratio[a]	Labeling Impact	Reference
AUC ≥ 1.25, with dosing recommendation				
Eluxadoline	13.74 (severe)	14.25 (severe)	Reduce dose (mild and moderate); contraindication (severe)	(FDA, 2015u)
Flibanserin	4.53 (mild)	0.91 (mild)	Contraindication (any HI)	(FDA, 2015a)
Lenvatinib	2.57 (severe)	0.54 (severe)	Reduce dose (severe)	(FDA, 2015p)
Isavuconazonium sulfate	Isavuconazole: 2.19 (moderate)[b]	Isavuconazole: 0.77 (moderate)[b]	Not recommended (severe)	(FDA, 2015g)
Panobinostat	2.05 (moderate)	1.83 (moderate)	Reduce dose (mild and moderate); avoid use (severe)	(FDA, 2015j)
Selexipag	4 (moderate); ACT-333679: 2 (moderate)	N/P	Avoid use (severe)	(FDA, 2015af)
Sacubitril	3.45 (moderate); LBQ657: 1.9 (moderate)	N/P	Reduce dose (moderate); not recommended (severe)	(FDA, 2015i)
Lumacaftor	1.50 (moderate)	1.30 (moderate)	Reduce dose (moderate and severe)	(FDA, 2015ad)
Brexpiprazole	1.46 (moderate)	0.76 (moderate)	Reduce dose (moderate and severe)	(FDA, 2015j)
Lesinurad	1.33 (moderate)	1.08 (moderate)	Not recommended (severe)	(FDA, 2015ag)
Ixazomib citrate	Ixazomib: 1.27 (moderate)	Ixazomib: 1.21 (moderate)	Reduce dose (moderate, severe)	(FDA, 2015ac)
Edoxaban	0.95 (mild); metabolite M4: 1.25	0.9 (mild); metabolite M4: 1.1	Not recommended (moderate and severe)	(FDA, 2015q)

	(mild)	(mild)		
AUC ratio < 1.25, with dosing recommendation				
Rolapitant	1.04 (moderate)	0.77 (moderate)	Avoid use (severe)	(FDA, 2015s)
Cariprazine	1.15 (moderate)	1.14 (moderate)	Not recommended (severe)	(FDA, 2015v)
Tenofovir alafenamide fumarate	0.92 (mild); tenofovir: 0.89 (mild)	N/P	Not recommended (severe)	(FDA, 2015aa)
No dedicated HI study, with dosing recommendation				
Ivabradine	N/T	N/T	Contraindication (severe)	(FDA, 2015f)
PMR Requested				
Palbociclib	N/T	N/T		(FDA, 2015k)
Trabectedin	N/T	N/T		(FDA, 2015x)
Cobimetinib	N/T	N/T		(FDA, 2015z)
Osimertinib	N/T	N/T		(FDA, 2015ae)
Alectinib	N/T	N/T		(FDA, 2015b)

AUC and C_{max} ratios presented were calculated by the DIDB Editorial Team using mean AUC and C_{max} values available in the NDA review documents and may differ from those presented in the product label; N/P – not provided; N/T – not tested.

[a] – The C_{max} ratios presented are for the same patient population as the maximal AUC ratio

[b] – Drug was given intravenously

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Table 11. NMEs with RI-related labeling impact

Drug name	Max AUC Ratio	C_{max} Ratio[a]	Labeling Impact	Reference
AUC ≥ 1.25, with dosing recommendation				
Avibactam	19.55 (ESRD)	1.40 (ESRD)	Reduce dose (moderate, severe and ESRD)	(FDA, 2015d)
Sugammadex	17.24 (severe to ESRD)	Not Provided	Not recommended (severe)	(FDA, 2015y)
Tenofovir alafenamide fumarate	1.92 (severe); tenofovir: 6.05 (severe)	1.83 (severe); tenofovir: 2.78 (severe)	Not recommended (severe)	(FDA, 2015aa)
Edoxaban	1.93 (ESRD); metabolite M4: 4.5 (ESRD)	0.93 (ESRD); metabolite M4: 2.0 (ESRD)	Reduce dose (15-50 mL/min); not recommended (CrCL < 15 mL/min)	(FDA, 2015q)
Sacubitril	1.30 (severe); LBQ657: 2.7 (severe)	N/P	Reduce dose (severe)	(FDA, 2015i)
Lesinurad	2.13 (severe)	1.14 (severe)	Contraindication (severe and ESRD)	(FDA, 2015ag)
Brexpiprazole	1.85 (severe)	1.00 (severe)	Reduce dose (moderate, severe and ESRD)	(FDA, 2015p)
Lenvatinib	1.66 (severe)	0.95 (severe)	Reduce dose (severe)	(FDA, 2015m)
Ixazomib citrate	1.41 (severe)	1.76 (severe)	Reduce dose (severe and ESRD)	(FDA, 2015ac)
AUC ratio < 1.25, with dosing recommendation				
No dedicated RI study, with dosing recommendation				
Lumacaftor	N/T	N/T	Exercise caution (severe and ESRD)	(FDA, 2015ad)

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Cariprazine	N/T	N/T	Not recommended (severe)	(FDA, 2015v)
Tipiracil	1.65 (moderate; population PK)	N/T	Adjust dose (moderate)	(FDA, 2015n)
Cholic acid[b]	N/T	N/T	The urinary excretion of atypical bile acids maybe reduced in renal impaired patients.	(FDA, 2015e)
PMR Requested				
Eluxadoline	N/T	N/T		(FDA, 2015u)

AUC and C_{max} ratios presented were calculated by the DIDB Editorial Team using mean AUC and C_{max} values available in the NDA review documents and may differ from those presented in the product label; N/P – not provided; N/T – not tested.

[a] – The C_{max} ratios presented are for the same patient population as the maximal AUC ratio

[b] – Labeling recommendations are extracted from the Clinical Pharmacology and Biopharmaceutics Review(s)

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Figure 1

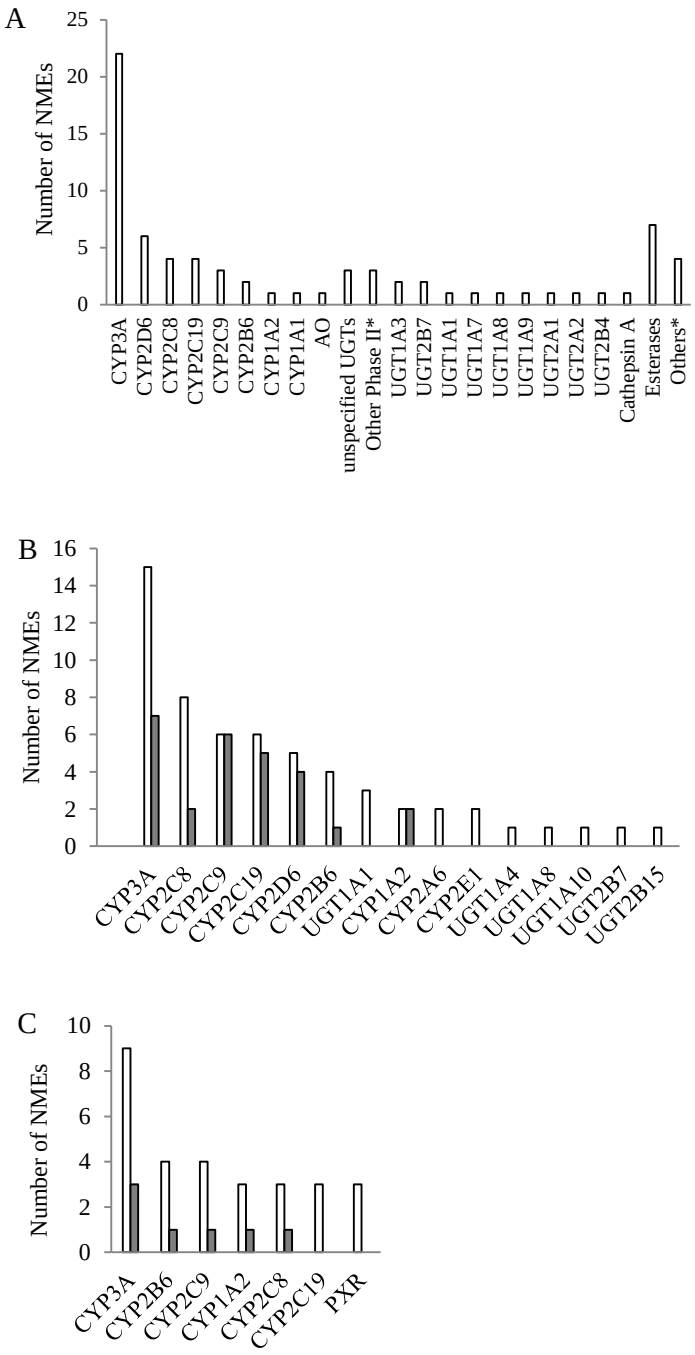

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Figure 2