Title

Risk of Clinically Relevant Pharmacokinetic-based Drug-drug Interactions with Drugs Approved by the U.S. Food and Drug Administration Between 2013 and 2016

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Running Title Page

a) Running title: A review of PK-based DDIs in 2013-2016 NDAs

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d) Abbreviations:

AUC, area under the time-plasma concentration curve; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CNS, central nervous system; \( C_{\text{max}} \), 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; FDC, fixed-dose combination; IM, intermediate metabolizer; NTR, narrow therapeutic range; NDA, new drug application; NME, new molecular entity; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; P450, cytochrome P450; PBPK, physiologically-based pharmacokinetics, PGx, pharmacogenetic(s); P-gp, P-glycoprotein; PK, pharmacokinetic(s); PM, poor metabolizer; PMR, post-marketing requirement; UGT, UDP-glucuronosyltransferase; UM, ultrarapid metabolizer
Abstract

A total of 103 drugs (including 14 combination drugs) were approved by the U.S. Food and Drug Administration from 2013 to 2016. Pharmacokinetic-based drug interaction profiles were analyzed using the University of Washington Drug Interaction Database and the clinical relevance of these observations was characterized based on information from New Drug Application reviews. CYP3A was involved in approximately 2/3 of all drug-drug interactions (DDIs). Transporters (alone or with enzymes) participated in about half of all interactions, but most of these were weak-to-moderate interactions. When considered as victims, eight new molecular entities (NMEs; cobimetinib, ibrutinib, isavuconazole, ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax) were identified as sensitive substrates of CYP3A, two NMEs (pirfenidone and tasimelteon) were sensitive substrates of CYP1A2, one NME (dasabuvir) was a sensitive substrate of CYP2C8, one NME (eliglustat) was a sensitive substrate of CYP2D6, and one NME (grazoprevir) was a sensitive substrate of OATP1B1/3 (with changes in exposure greater than 5-fold when co-administered with a strong inhibitor). Approximately 75% of identified CYP3A substrates were also substrates of P-gp. As perpetrators, most clinical DDIs involved weak-to-moderate inhibition or induction. Only idelalisib showed strong inhibition of CYP3A, and lumacaftor behaved as a strong CYP3A inducer. Among drugs with large changes in exposure (≥ 5-fold), whether as victim or perpetrator, the most represented therapeutic classes were antivirals and oncology drugs, suggesting a significant risk of clinical DDIs in these patient populations.
Introduction

Pharmacokinetic (PK)-based drug-drug interactions (DDIs) constitute one of the major causes of drug withdrawal from the market in recent decades (Huang et al., 2008). Mechanistic methodologies have been utilized by the pharmaceutical industry to assess DDI risk during the drug development process. Currently, these methodologies include evaluation of the potential of a new molecular entity (NME) to affect the metabolism or transport of other drugs and the potential for the new drug’s metabolism or transport to be affected by other drugs, with recommended clinical index substrates and specific inhibitors/inducers of drug metabolizing enzymes (DMEs) or transporters (FDA; FDA, 2012a). Additionally, if a NME is commonly used with another drug in a designated patient population, it is recommended that the DDI risk between the two drugs be evaluated. This review encompasses a detailed analysis of clinical DDIs mediated by DMEs and transporters based on New Drug Applications (NDAs) approved by the U.S. FDA from 2013 to 2016. It highlights main mechanistic findings and discusses their clinical relevance, identifying substrates with varying degrees of sensitivity and inhibitors/inducers with varying potency of DMEs and transporters and how these findings are reflected in the labeling. These findings will aid to understand, predict, and reduce DDI risk and associated adverse reactions in certain patient populations, in which poly-therapy is common. Through systematic analysis, this review aimed to provide communications on DDI risk evaluation and management as well as clinical implications to pharmaceutical researchers and health care providers.

Methods

This analysis was performed using the University of Washington Drug Interaction Database® (DIDB®) drug interactions and pharmacogenetics (PGx) database, (http://www.druginteractioninfo.org). Clinical DDI study results included in this analysis were generated from dedicated DDI clinical trials, PGx studies, as well as physiologically-based pharmacokinetics (PBPK) simulations that are used as alternatives to dedicated clinical studies. As in previous publications, mean area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) ratios that are systematically presented by
the DIDB are the metrics used to evaluate clinical studies. In the present analysis, all positive clinical studies (defined as AUC ratios ≥ 1.25 for inhibition and ≤ 0.8 for induction) were analyzed. Because a 2-fold change in drug exposure often triggers dose recommendations, all DDI studies with exposure changes ≥ 2-fold were highlighted regardless of labeling effects. Also, studies with drug exposure changes of 1.25- to 2-fold and still triggering dose recommendations are presented. In accordance with the FDA classification (FDA, 2012a), NMEs were considered as sensitive or moderate sensitive clinical substrates if they demonstrated maximum AUC ratios of ≥ 5 or 2-5, respectively, with strong inhibitors of a given metabolic pathway. Therefore, in this review, the DDI results were presented based on inhibition studies when NMEs were evaluated as substrates, with additional evidence from drug interaction studies using strong inducers. On the other hand, an NME was considered as a strong, moderate, or weak clinical inhibitor or inducer (of a given disposition pathway) when the observed maximum AUC ratio was ≥ 5, 2-5, and 1.25-2, respectively, for inhibitors, and ≤ 0.2, 0.2-0.5, and 0.5-0.8, respectively, for inducers, with co-administration of a sensitive clinical substrate.

Results

From 2013 to 2016, a total of 103 NDAs (including 14 combination drugs, total NMEs = 107; Supplemental Table 1, with chemical structures presented in Supplemental Table 2 for drugs approved in 2016 and previous publications (Yu et al., 2014; Yu et al., 2016; Yu et al., 2017) for drugs approved from 2013 to 2015) and 32 Biologics License Applications were approved by the FDA. Because of the different disposition and elimination mechanisms of biologics compared to small molecules and their low risk for PK-based drug interactions, Biologics License Applications contain few studies relevant to the present analysis and were not included in this review. Among all the NDAs included in the analysis, the most represented therapeutic areas were oncology (21%) and anti-infective drugs (20%), followed by central nervous system (CNS) agents (13%), metabolism disorder/endocrinology drugs (11%), and cardiovascular drugs (10%). Among the anti-infective drugs (N = 21), there are 10 antivirals, six antibacterials, four antifungals, and one anti-parasitic. Ninety-eight of the 103 NDAs had drug
metabolism data and 81 had transporter data available, including in vitro and/or clinical evaluations. NDAs for all years analyzed included extensive in vitro evaluations of drug metabolism profiles ranging from 88% (in 2013) to 100% of the NDAs (in 2014). There was an increase in the percentage of NDAs that included assessment of in vitro transport from 73 - 80% evaluated between 2013 and 2015 to 93% evaluated in 2016. In particular, the number of transporter experiments per drug increased dramatically in the past four years, from 6 in 2013 to 22 in 2016. The types of transporters evaluated also expanded from 16 (in 2013) to 21 (in 2016). In addition to the nine transporters recommended by the FDA draft guidance (FDA, 2012a) and the International Transporter Consortium White Paper (Hillgren et al., 2013), 18 other transporters were assessed in the NDAs. Transporters evaluated in these NDAs included apical sodium dependent bile acid transporter (ASBT), bile salt export pump (BSEP), breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein 1/2-K (MATE1, MATE2-K), multidrug resistance-associated protein 1/2/3/4/5/8 (MRP1, MRP2, MRP3, MRP4, MRP5, MRP8), organic anion transporter 1/2/3/4 (OAT1, OAT2, OAT3, OAT4), organic anion transporting polypeptide 1A2/1B1/1B3/2B1 (OATP1A2, OATP1B1, OATP1B3, OATP2B1), organic cation transporter 1/2/3 (OCT1, OCT2, OCT3), organic cation/carnitine transporter 1/2 (OCTN1, OCTN2), P-glycoprotein (P-gp), sodium-taurocholate co-transporting polypeptide (NTCP), and urate transporter 1 (URAT1). Finally, in addition to clinical DDI studies, 16 NDAs presented PGx information, and 16 had PBPK simulation data that directly supported dosing recommendations. An analysis of clinically relevant DDI findings and related in vitro investigations is presented in the following sections. Key DDI findings are summarized in Tables 1-4, including maximum AUC ratios, enzymes and transporters possibly involved, and overall labeling impact. For each interaction, more detailed information such as dosing regimen for victim and precipitant drugs, study design, study population, and specific labeling impact is presented in Supplemental Tables 3-6.

NMEs as Substrates
Overall, for drugs evaluated as substrates, there were approximately 100 inhibition studies with AUC ratios ≥ 2 and 50 induction studies with AUC ratios ≤ 0.5 with concomitant administration of inhibitors and inducers, respectively. Additionally, approximately 30 inhibition studies with AUC ratios of 1.25-2 and 10 induction studies with AUC ratios of 0.5-0.8 were associated with dose recommendations included in the drug label. A total of 53 NMEs served as victim drugs in these interaction studies. Of these drugs, cancer treatments and antivirals are the dominant therapeutic areas (Figures 1A and 2A).

**DDIs with AUC changes ≥ 5-fold: sensitive clinical substrates**

When NMEs served as victims, 14 drugs were found to have AUC ratios ≥ 5 when co-administered with strong inhibitors (Table 1 and Supplemental Table 3). In terms of therapeutic classes, the most represented area is anti-infective agents (36%), including four antivirals and one antifungal, followed by cancer treatments (N = 3, 21%) and CNS agents (N = 2, 14%) (Supplemental Figure 1A). This pattern of prevalence is consistent among drugs approved from 2013 to 2016.

The highest AUC change was observed with the antiviral paritaprevir that exhibited a 47.43-fold increase in the presence of ritonavir (100 mg single dose, not a NME), a strong inhibitor of CYP3A (also an inhibitor of multiple transporters). This DDI effect was observed in a fixed-dose combination (FDC) drug (ombitasvir/paritaprevir/ritonavir co-packaged with dasabuvir), where paritaprevir is administered at low dose (100 mg) and the role of ritonavir is to increase paritaprevir peak and trough concentrations as well as its overall drug exposure.

Eliglustat, a glucosylceramide synthase inhibitor indicated for the treatment of Gaucher disease, exhibited the second largest DDI effect, wherein the strong CYP2D6 inhibitor paroxetine (30 mg once daily for 10 days) significantly increased eliglustat AUC 28.40-fold in CYP2D6 ultrarapid metabolizer (UM) subjects. Increases of 10.00- and 5.20-fold were observed in CYP2D6 extensive metabolizers (EMs) and intermediate metabolizers (IMs), respectively, when eliglustat was co-administered with paroxetine. Consistent with these findings, the exposure to eliglustat (100 mg twice daily) was 2.60-fold higher in IMs, 7.80-fold higher in poor metabolizers (PMs), and lower by 85.6% in UMs, compared to CYP2D6
EM subjects. Based on these observations, genetic testing is considered necessary before administering eliglustat and dose adjustment is needed depending on CYP2D6 polymorphism and/or co-administration with a strong or moderate CYP2D6 inhibitor (FDA, 2014c).

Regarding possible mechanism(s) of these large interactions, significant changes in victim drug exposure could be attributed to one or more of the following DMEs and transporters, CYP1A2, CYP2C8, CYP2D6, CYP3A, BCRP, OATP1B1/3, and P-gp (Supplemental Figure 1B). CYP3A was involved in 2/3 of the drug interactions, either as main contributor or together with other P450s or transporters. Eight drugs in this group, cobimetinib, ibrutinib, isavuconazole (the active metabolite of prodrug isavuconazonium sulfate) ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax were identified as sensitive clinical substrates of CYP3A, with AUC ratios of 6.62, 23.90, 5.22, 7.70, 12.42, 47.43, 7.18, and 6.40, respectively, when co-administered with strong CYP3A inhibitors such as itraconazole, ketoconazole or ritonavir. For cobimetinib, ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax, contributions of P-gp are possible as in vitro studies showed that they are all substrates of P-gp (FDA, 2014h; FDA, 2014c; FDA, 2015c; FDA, 2015d), and itraconazole, ketoconazole, and ritonavir are known inhibitors of P-gp (FDA; FDA, 1996). Further, OATP1B1/3 (and possibly BCRP) may also be a factor in the interaction between paritaprevir and ritonavir. Due to a lack of specific inhibitors, it remains challenging to identify the exact contribution of each enzyme or transporter to drug disposition. On the other hand, these eight drugs are also sensitive to induction. Co-administration of the strong CYP3A inducers carbamazepine (for paritaprevir), rifampin (for cobimetinib, ibrutinib, isavuconazole, naloxegol, and venetoclax), or St. John’s Wort (for ivabradine PBPK simulations) or the moderate inducer efavirenz (for simeprevir) significantly reduced drug exposure by 70-97%, suggesting a reduction in therapeutic efficacy (FDA, 2013i; FDA, 2014m; FDA, 2015c) (Tables 2 and Supplemental Table 4). In addition to being substrates of CYP3A, four of these drugs were identified as sensitive clinical substrates of other P450s--pirfenidone and tasimelteon of CYP1A2, dasabuvir of CYP2C8, and eliglustat of CYP2D6. The plasma exposure of pirfenidone, tasimelteon, dasabuvir, and eliglustat increased 6.81-, 6.87-, 9.90-, and
28.40-fold when co-administered with the strong clinical inhibitors fluvoxamine, gemfibrozil, and paroxetine, respectively (FDA, 2014d; FDA, 2014f; FDA, 2014m; FDA, 2014c). In vitro studies showed that tasimelteon is also metabolized by CYP3A (FDA, 2014f) and fluvoxamine is a weak inhibitor of CYP3A (Lam et al., 2003). However, co-administration of ketoconazole (strong CYP3A inhibitor), only slightly increased tasimelteon AUC (by 45%), suggesting that inhibition of CYP3A-mediated metabolism of tasimelteon by fluvoxamine is negligible (FDA, 2014f). A 6.41-fold increase in flibanserin exposure was observed when co-administered with fluconazole, a strong CYP2C19 inhibitor and also a moderate CYP3A inhibitor, while a smaller change (4.61-fold) was observed with co-administration of the strong CYP3A inhibitor ketoconazole, suggesting that CYP3A plays a primary role in the disposition of flibanserin with partial contribution from CYP2C19, but flibanserin is not a sensitive substrate of CYP3A (FDA, 2015a).

In addition to metabolism, transporters seem to play an important role in some cases. For example, in vitro studies suggest that grazoprevir is a substrate of OATP1B1/3, BCRP, and P-gp (FDA, 2016f). Grazoprevir exposure was increased 10.22-fold with concomitant administration of intravenous rifampin, a clinical inhibitor of OATP1B1/3, suggesting that grazoprevir is a sensitive clinical substrate of OATP1B1/3. A 15.25-fold increase in grazoprevir AUC was observed when co-administered with the multi-transporter inhibitor cyclosporine, suggesting an involvement of BCRP and P-gp in addition to OATP (FDA, 2016f).

Consistent with the large changes in drug exposure observed with these 14 drugs (13 identified as sensitive substrates), their product labels included clinical recommendations (contraindicate, avoid, not recommend, or reduce the dose).

**DDIs with 2 ≤ AUC ratios < 5: moderate sensitive clinical substrates**

A total of 28 drugs (including 8 drugs overlapping with the group of AUC ratios ≥ 5) demonstrated AUC increases of 2- to 5-fold when co-administered with inhibitors of enzymes and/or transporters. Detailed DDI data is presented in Supplemental Table 3. The majority of these DDIs were addressed in the product
labeling, mostly with a recommendation to avoid co-administration or to reduce the dose. The largest number of drugs in this group are antivirals (N = 8), followed by cardiovascular drugs (N = 5), CNS agents (N = 5), cancer treatments (N = 4), and gastrointestinal agents (N = 3) (Supplemental Figure 1C). In brief, among the 32 drug interactions identified in this group, the majority is attributable to inhibition of one enzyme or transporter by strong inhibitors (Supplemental Figure 1D), therefore the NMEs are considered moderate sensitive substrates in accordance with the FDA classification and terminology (FDA, 2012a). CYP3A plays a dominant role by mediating 2/3 of the drug interactions. Interestingly, P-gp, BCRP, and OATP1B1/3 are involved in approximately 1/3 of these interactions either as an individual contributor or together with other transporters or CYP3A (Supplemental Figure 1D). Changes in victim exposure appeared to be no larger than 3-fold for most interactions.

**DDIs with 1.25 ≤ AUC ratios < 2 and triggering dose recommendations**

As victims, 21 NMEs (five overlapping with the AUC ratio ≥ 5 group, three overlapping with the AUC ratios between 2-5 group, and one overlapping with both groups) were found to have slight increases of less than 2-fold in their exposure when co-administered with inhibitors; however, label recommendations were triggered due to safety concerns (Supplemental Table 3). In most of these cases, the labels included recommendations to monitor drug exposure and/or patients for increased drug exposure associated adverse reactions and/or reduce dose. The most represented drug areas are cancer treatments (N = 8) and antivirals (N = 4) (Supplemental Figure 1E).

CYP3A was again found to be a significant contributor, mediating more than 60% of the interactions, partially with contributions from other P450s or P-gp/OATP1B1/3 (Supplemental Figure 1F). However, CYP3A does not seem to play a primary role in the drug disposition of the following NMEs: dabrafenib, dasabuvir, idelalisib, nintedanib, ospemifene, palbociclib, panobinostat, trabectedin, vilanterol, and vorapaxar.

Different label recommendations were triggered on the basis of different DDI scenarios. For example, as discussed above, venetoclax was identified as a sensitive CYP3A substrate through an interaction study.
with ketoconazole, a strong CYP3A inhibitor. Due to the large increase in venetoclax exposure, concomitant use of venetoclax with strong CYP3A inhibitors is contraindicated or venetoclax dose reduction is recommended depending on different treatment phase (FDA, 2016e). When co-administered with moderate CYP3A inhibitors, such as ciprofloxacin, diltiazem, or fluconazole, a 40-60% increase was observed in venetoclax exposure. Considering the risk of toxicities associated with increased exposure, concomitant use of venetoclax with moderate CYP3A inhibitors should also be avoided. If a moderate CYP3A inhibitor must be used, the dose of venetoclax should be reduced by at least 50%, and patients need to be monitored closely for signs of toxicities (FDA, 2016e). Exposure to venetoclax was not affected by co-administration of weak CYP3A inhibitors. Additionally, a 600 mg single dose of rifampin increased venetoclax AUC by 78% and $C_{\text{max}}$ by 113%, likely by inhibiting P-gp-mediated efflux of venetoclax. Labeling recommendations similar to those with moderate CYP3A inhibitors were proposed for concomitant use of venetoclax with P-gp inhibitors (FDA, 2016e).

**In vitro-in vivo considerations for NMEs as substrates**

Overall, when all NMEs were evaluated as substrates, CYP3A and P-gp were involved to some degree in approximately 65% and 30% of all clinical interactions, respectively. When evaluated in vitro, CYP3A4/5 was shown to metabolize 64 NMEs (Figure 5A). Of these, 39 NMEs were confirmed in vivo (systemic exposure increases $\geq 25\%$) when co-administered with strong or moderate CYP3A inhibitors. All the drugs with the exception of velpatasvir and netupitant included dosing recommendations in their labeling pertaining to inhibition and/or induction of CYP3A. With regard to P-gp, a total of 47 NMEs were shown to be substrates of P-gp in vitro (more than any other transporter) (Figure 5B) and 74% of the clinical CYP3A substrates (29 out of 39 drugs) were shown to be substrates of P-gp in vitro. Twenty-six NMEs were further evaluated in vivo, and 21 showed positive results with AUC ratios of 1.25-7.70. However, among DDIs with large changes of $\geq 5\text{-fold}$ in victim exposure, the role of P-gp is unclear since the affected drugs were either substrates of CYP3A or OATP1B1/3.

**NMEs as Inhibitors**
When NMEs were evaluated as inhibitors, 20 drugs were found to show clinically relevant inhibition, with approximately 40 DDIs presenting AUC ratios $\geq 2$ and 50 DDIs presenting AUC ratios of 1.25-2 and triggering dose recommendations. Among these drugs, the most represented therapeutic areas are anti-infective agents (N = 8), including six antivirals, one antibacterial, and one antifungal, followed by cancer treatments (N = 4), CNS drugs (N = 3), gastrointestinal agents (N = 3), and metabolism disorder/endocrinology treatments (N = 2) (Figure 3A).

**DDIs with AUC ratios $\geq 5$: strong clinical inhibitors**

Only two drugs, the antiviral FDC drug Viekira Pak (paritaprevir, ritonavir, ombitasvir, and dasabuvir) and the kinase inhibitor idelalisib were found to cause strong inhibition, increasing exposure of victim drugs $\geq 5$-fold (Table 3 and Supplemental Table 5). CYP3A was the only enzyme affected, with partial contribution by P-gp. The largest change in exposure was observed with Viekira Pak (paritaprevir/ritonavir 150/100 mg once daily + ombitasvir 25 mg once daily + dasabuvir 400 mg twice daily for 28 days), showing a drastic increase in tacrolimus exposure with an AUC ratio of 57.07. Similarly, an approximately 5-fold increase in cyclosporine (a CYP3A and P-gp substrate) exposure was observed when co-administered with Viekira Pak. Considering the risks associated with large increases in exposure of tacrolimus and cyclosporine, significant dose adjustment and close monitoring of their blood concentrations are recommended for both immunosuppressants when co-administered with Viekira Pak (FDA, 2014m). Since the strong inhibition by Viekira Pak is caused by ritonavir which is not a NME, this FDC drug is not counted as a strong inhibitor in this analysis. A larger increase in tacrolimus exposure, 80-fold AUC increase, was observed when ritonavir was combined with paritaprevir/ombitasvir or paritaprevir/dasabuvir for 28 days. Idelalisib showed strong inhibition of CYP3A, increasing the AUC of midazolam 5.15-fold. Consequently, co-administration of idelalisib with CYP3A substrates should be avoided (FDA, 2014o) and idelalisib is considered a strong inhibitor of CYP3A.

**DDIs with 2 $\leq$ AUC ratios $< 5$: moderate clinical inhibitors**
When NMEs served as inhibitors, a total of 36 DDIs showed increases in exposure of victim drugs of 2- to 5-fold perpetrated by 12 drugs (including FDC drugs, so total NME = 15). Among these, five drugs (including 8 NMEs) are antivirals (Supplemental Figure 3A). Detailed DDI data are presented in Supplemental Table 5. Briefly, transporters including BCRP, OATP1B1/3, and P-gp seem to play an important role, mediating half of the interactions (Supplemental Figure 3B). However, due to a lack of substrate specificity, many interactions cannot be attributed to a specific transporter. CYP3A was involved in the drug interactions of four drugs, either as a single contributor or together with P-gp. In addition to P450 enzymes, UGT1A1 also participated in two drug interactions. It is worth noting that the three antiviral FDC drugs identified as moderate inhibitors (Harvoni, Viekira Pak, and Zepatier) presented complex inhibition scenarios because each component itself is a clinical inhibitor of multiple enzymes and/or transporters.

DDIs with $1.25 \leq \text{AUC ratios} < 2$ and triggering dose recommendations: weak clinical inhibitors

Compared to the number of drugs that showed strong and moderate inhibition, more drugs showed weak inhibition and also triggered dose recommendations. Indeed, from approximately 50 DDI studies, a total of 20 NMEs (including three FDC drugs) showed less than 2-fold increases in exposure of victim drugs and labeling recommendations were made based on these observations (Supplemental Table 5). The most represented drugs are anti-infective agents, including six antivirals, one antibacterial, and one antifungal (Supplemental Figure 3C).

Transporters mediated half of these weak interactions, most of them attributable to inhibition of P-gp, followed by OATP1B1/3 (Supplemental Figure 3D). Increases in plasma exposure of digoxin, a clinical substrate of P-gp and also a NTR drug, appear to be a major concern for DDIs relevant to inhibition of P-gp. Eight drugs, including daclatasvir, eliglustat, flibanserin, isavuconazonium sulfate (prodrug), rolapitant, simeprevir, suvorexant, and velpatasvir, increased the exposure of co-administered digoxin, with AUC and $C_{\text{max}}$ ratios of 1.25-1.93. Consequently, it was recommended to monitor digoxin (and other P-gp substrates with a NTR) concentrations and adverse reactions, and adjust digoxin doses if necessary,
upon co-administration with any of these drugs (FDA, 2013i; FDA, 2014c; FDA, 2014b; FDA, 2015f; FDA, 2015a; FDA, 2015e; FDA, 2015o; FDA, 2016b). Regarding OATP1B1/3-mediated interactions, most involved the HMG-CoA reductase inhibitors atorvastatin, pravastatin, rosuvastatin, and simvastatin as victims. Increased risk of myopathy associated with higher statin concentrations is the main reason triggering labeling recommendations. Dose reduction of statins and close monitoring for statin-associated adverse reactions are recommended for the following drugs: daclatasvir, elbasvir/grazoprevir, eluxadoline, grazoprevir, simeprevir, and Viekira Pak (FDA, 2013i; FDA, 2014m; FDA, 2015f; FDA, 2015p; FDA, 2016f). The second largest group of DDIs was mediated by CYP3A. For example, midazolam exposure was increased by 58, 43, and 47% when co-administered with palbociclib, simeprevir, or suvorexant, respectively. Consequently, a dose reduction is recommended for palbociclib, while caution and close monitoring of patients are warranted for simeprevir and suvorexant, when co-administered with sensitive CYP3A substrate with a NTR (FDA, 2013i; FDA, 2014b; FDA, 2015h). As discussed above, isavuconazonium sulfate (prodrug) was identified as a moderate inhibitor of CYP3A, with 103 and 125% increases observed in the exposure of co-administered midazolam or tacrolimus (both sensitive CYP3A substrates), respectively. A smaller increase (84%) was observed in sirolimus exposure (also a sensitive CYP3A substrate), while relatively weaker inhibition was observed when it was co-administered with atorvastatin (a moderate sensitive CYP3A substrate) or cyclosporine (a CYP3A substrate with a NTR), with 40 and 30% increases in victim drug exposure, respectively.

In vitro-in vivo considerations for NMEs as inhibitors

Overall, when all NMEs were evaluated as inhibitors, CYP3A and P-gp played a dominant role mediating approximately 60% (30% each) of all the interactions, followed by OATP1B1/3. As observed in previous years (Yu et al., 2014; Yu et al., 2016; Yu et al., 2017), the majority of the NMEs were extensively evaluated in vitro for their inhibition potential of DMEs and transporters. If an inhibitory effect was observed within the tested concentration range as provided in the NDA reviews, the NME was considered to show positive inhibition in vitro. Following regulatory recommendations described in the FDA draft
guidance (FDA, 2012a), an in vitro to in vivo prediction estimate was calculated for major DMEs and transporters. Most drugs with higher [I]/IC$_{50}$, [I]/K$_{i}$, or R values than the cut-off were moved forward for clinical evaluations or alternative PBPK simulations. Not surprisingly, CYP3A was the most often inhibited enzyme in vitro. However, while 47 NMEs showed positive inhibition of CYP3A in vitro (Figure 6A), only 15 drugs (32%) presented clinical inhibition with ≥ 1.25-fold increase in the exposure of co-administered CYP3A substrate. With regard to transporters, 41 were in vitro inhibitors of OATP1B1 and 34 were inhibitors of OATP1B3 in vitro (Figure 6B). When evaluated in vivo, only 10 of these drugs were identified as clinical inhibitors of OATP1B1/3, increasing the exposure of OATP1B1/3 substrate by ≥ 25%. In terms of P-gp, 37 NMEs were found to inhibit P-gp in vitro (Figure 6B) and 23 drugs were further evaluated in vivo (including one that was evaluated using PBPK simulations). Only 14 drugs showed positive inhibition in vivo, with ≥ 1.25-fold increase in the exposure of co-administered P-gp substrate. Likewise, for BCRP, a total of 34 NMEs were found to be inhibitors of BCRP in vitro (Figure 6B), while only 10 were confirmed to inhibit this transporter to a clinically relevant extent, with an AUC ratio ≥ 1.25 when co-administered with a BCRP substrate. These observations highlight the gap between in vitro-based predictions and clinical evaluation results, since quite a few drugs with a predicted potential risk were not clinically relevant inhibitors, suggesting a need to improve the current prediction models.

**NMEs as Inducers**

As perpetrators, only seven NMEs (including one FDC drug) showed clinically relevant induction (Table 4 and Supplemental Table 6). Among them, three drugs are anti-infectives, including one antibacterial (oritavancin), one antifungal (isavuconazonium sulfate), and one antiviral (Viekira Pak) (Figure 4A). The largest change in victim drug exposure was observed with lumacaftor, which significantly decreased the AUC of ivacaftor, a sensitive CYP3A substrate (FDA, 2012b) by 80% (lumacaftor and ivacaftor are two components of a combination drug for the treatment of cystic fibrosis). Interestingly, a similar exposure change was observed in itraconazole when it was co-administered with the ivacaftor/lumacaftor (250
mg/200 mg twice daily for 7 days). Based on this observation, co-administration of this combination drug with sensitive CYP3A substrates or CYP3A substrates with a NTR is not recommended. Additionally, hormonal contraceptives (CYP3A substrates) should not be relied upon as an effective method of contraception (FDA, 2015k). The second largest induction was presented by dabrafenib, reducing the AUC of midazolam by 74%. Consequently, it was noted in the label that concomitant use of dabrafenib with drugs that are sensitive substrates of CYP3A may result in loss of efficacy (FDA, 2013m). In accordance with the FDA guidance (FDA, 2012a), lumacaftor and dabrafenib were identified as strong and moderate CYP3A inducers, respectively. Five drugs, eslicarbazepine acetate, isavuconazonium sulfate, lesinurad, oritavancin, and Viekira Pak (induction mainly caused by ritonavir, which is not an NME) were found to show weak induction (AUC ratios of 0.5-0.8) but still triggered labeling recommendations. Not surprisingly, most of the interactions were mediated by CYP3A. However, induction of other P450s was also observed with the three anti-infective drugs, isavuconazonium sulfate (200 mg once daily), Viekira Pak (paritaprevir/ritonavir 150/100 mg once daily + ombitasvir 25 mg once daily + dasabuvir 250 mg twice daily for 19 days), and oritavancin (1200 mg intravenously), which decreased the AUC of co-administered bupropion (CYP2B6 sensitive substrate), omeprazole (CYP2C19 sensitive substrate), and dextromethorphan (CYP2D6 sensitive substrate) by 42, 38, and 31% (concentration ratio of dextromethorphan to dextrorphan in urine), respectively. Interestingly, eslicarbazepine acetate caused a 35% reduction in rosuvastatin AUC and $C_{\text{max}}$, which maybe attributable to induction of OATP1B1/3 and/or BCRP. However, there is no in vitro evidence available to fully understand the mechanism.

In vitro evaluation showed that 24 NMEs induced CYP3A, while 15 and eight NMEs induced CYP2B6 and CYP1A2, respectively. Activation of the pregnane X receptor was evaluated for some drugs and eight NMEs were found to activate this nuclear receptor to some extent (Figure 7). Dabrafenib, lesinurab, and paritaprevir all showed induction of CYP3A, while isavuconazole (the active metabolite of isavuconazonium sulfate) induced both CYP2B6 and CYP3A at clinically relevant concentrations.
However, the in vitro enzyme induction potential of eslicarbazepine is not conclusive based on the available data (Bialer et al., 2007; Bialer and Soares-da-Silva, 2012; FDA, 2013c; Zaccara et al., 2015).

**Discussion and Conclusion**

A detailed analysis of PK-based DDI data contained in the NDAs approved by the U.S. FDA in the past four years (from 2013-2016) was performed. Drug interaction profiles and clinical relevance of the outcomes were characterized. CYP3A was confirmed to be a major contributor to clinical DDIs involving NMEs as victims and/or perpetrators, which is consistent with what was found with all the drugs marketed in the past decades. Interestingly, it was found that transporter-based DDIs represented a significant number of all observed drug interactions (about 50%, with NMEs as either victims or inhibitors), although most of these were weak-to-moderate interactions. This also reflects the degree of involvement of transporters in DDI evaluations in the past few years.

Overall, when considered as victims, 13 NMEs were identified as sensitive substrates of CYP1A2 (pirfenidone and tasimelteon), CYP2C8 (dasabuvir), CYP2D6 (eliglustat), CYP3A (cobimetinib, ibrutinib, isavuconazole, ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax), or OATP1B1/3 (grazopervir), with changes in exposure equal to or greater than 5-fold when co-administered with a strong inhibitor. Among these sensitive substrates, approximately 40% are anti-infective agents and 22% are cancer treatment drugs, suggesting a significant risk of clinically relevant DDIs in these patient populations in which therapeutic management is already complex due to poly-therapy. These two classes of drugs are also the most represented therapeutics approved in the past four years, comprising approximately 40% of all the approved drugs. As expected, approximately 75% of drugs identified as CYP3A substrates were also substrates of P-gp, consistent with previous findings (Christians et al., 2005; Zhou et al., 2008). As perpetrators, most clinical DDIs involved weak-to-moderate inhibition or induction, with only one drug (idelalisib) showing strong inhibition of CYP3A, and one NME (lumacaftor) behaving as a strong clinical CYP3A inducer.
DMD # 78691

Not surprisingly, all the DDIs with exposure changes ≥ 5-fold in the victim drug were clearly addressed in their labels, mostly as contraindications and co-administration avoidance. There were approximately 125 DDIs with exposure changes (increases or decreases) of 2- to 5-fold with NMEs either as substrates of perpetrators, and over 80% of these effects triggered dose recommendations in the labels. Interestingly, most of the DDIs that were not reflected in the label pertained to antiviral co-medications and were mediated by transporters, such as P-gp and BCRP, functioning as a main or partial factor. For example, co-administration of sofosbuvir with simeprevir, valtapaavir, darunavir/ritonavir + emtricitabine + tenofovir DF, raltegravir + emtricitabine + tenofovir DF, or atazanavir/ritonavir + emtricitabine + tenofovir DF, increased the AUC of sofosbuvir 2- to 4-fold. However, considering the safety margins of sofosbuvir the increase in sofosbuvir exposure was not considered clinically relevant by the sponsor, therefore no dose adjustment is needed. It is worth noting that approximately 100 DDIs with AUC ratios of 1.25-2 (for inhibition) or 0.5-0.8 (for induction) resulted in labeling impact, with 52% related to drugs as substrates, 36% as inhibitors, and 12% as inducers. This is understandable because of majority of these interactions were NTR drugs for which small changes in drug exposure may increase the risk of adverse reactions or result in loss of efficacy. The number of DDIs of this group is comparable to that with AUC changes 2- to 5-fold that triggered dose recommendations. Given that a significant number of DDIs with smaller exposure changes triggered label recommendations, special attention should be given to DDIs for NTR drugs. Finally, 14 of the 103 recently approved drugs were combination drugs with highly complex drug interaction profiles in some cases, highlighting the continuous challenge of managing DDIs in clinical practice.

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DMD # 78691

Authorship Contributions

Participated in research design: Yu, Levy, Ragueneau-Majlessi

Performed data analysis: Yu, Zhou, Tay-Sontheimer, Levy, Ragueneau-Majlessi

Wrote or contributed to the writing of the manuscript: Yu, Zhou, Tay-Sontheimer, Levy, Ragueneau-Majlessi
References


FDA FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers


FDA (1996) Drug approval package: ALLEGRA (fexofenadine hydrochloride). FDA application NDA 020625. FDA, Silver Spring, MD.


FDA (2012b) Drug approval package: KALYDECO (ivacaftor). FDA application NDA 203188. FDA, Silver Spring, MD.

FDA (2013a) Drug approval package: ADEMPAS (riociguat). FDA application NDA 204819. FDA, Silver Spring, MD.

FDA (2013b) Drug approval package: ANORO ELLIPTA (umeclidinium and vilanterol). FDA application NDA 203975. FDA, Silver Spring, MD.
DMD # 78691

FDA (2013c) Drug approval package: APTIOM (eslicarbazepine acetate) FDA application NDA 022416. FDA, Silver Spring, MD.

FDA (2013d) Drug approval package: BREO ELLIPTA (fluticasone and vilanterol). FDA application NDA 204275. FDA, Silver Spring, MD.

FDA (2013e) Drug approval package: BRINTELLIX (vortioxetine). FDA application NDA 204447. FDA, Silver Spring, MD.

FDA (2013f) Drug approval package: GILOTRIF (afatinib). FDA application NDA 201192. FDA, Silver Spring, MD.

FDA (2013g) Drug approval package: IMBRUVICA (ibrutinib). FDA application NDA 205552. FDA, Silver Spring, MD.

FDA (2013h) Drug approval package: INVOKANA (canagliflozin). FDA application NDA 204042. FDA, Silver Spring, MD.

FDA (2013i) Drug approval package: OLYSIO (simeprevir). FDA application NDA 205123. FDA, Silver Spring, MD.

FDA (2013j) Drug approval package: OPSUMIT (macitentan). FDA application NDA 204410. FDA, Silver Spring, MD.

FDA (2013k) Drug approval package: OSPHENA (ospemifene). FDA application NDA 203505. FDA, Silver Spring, MD.

FDA (2013l) Drug approval package: SOVALDI (sofosbuvir). FDA application NDA 204671. FDA, Silver Spring, MD.

FDA (2013m) Drug approval package: TAFINLAR (dabrafenib). FDA application NDA 202806. FDA, Silver Spring, MD.

FDA (2013n) Drug approval package: TIVICAY (dolutegravir). FDA application NDA 204790. FDA, Silver Spring, MD.

FDA (2014a) Drug approval package: AKYNZE (netupitant and palonosetron). FDA application NDA 205718. FDA, Silver Spring, MD.
DMD # 78691

FDA (2014b) Drug approval package: BELSOMRA (suvorexant). FDA application NDA 204569. FDA, Silver Spring, MD.

FDA (2014c) Drug approval package: CERDELGA (eliglustat). FDA application NDA 205494. FDA, Silver Spring, MD.

FDA (2014d) Drug approval package: ESBRIET (pirfenidone). FDA application NDA 022535. FDA, Silver Spring, MD.

FDA (2014e) Drug approval package: HARVONI (ledipasvir and Sofosbuvir). FDA application NDA 205834. FDA, Silver Spring, MD.

FDA (2014f) Drug approval package: HETLIOZ (tasimelteon). FDA application NDA 205677. FDA, Silver Spring, MD.

FDA (2014g) Drug approval package: LYNPARZA (olaparib). FDA application NDA 206162. FDA, Silver Spring, MD.

FDA (2014h) Drug approval package: MOVANTIK (naloxegol). FDA application NDA 204760. FDA, Silver Spring, MD.

FDA (2014i) Drug approval package: NORTHERA (droxidopa). FDA application NDA 203202. FDA, Silver Spring, MD.

FDA (2014j) Drug approval package: OFEV (nintedanib). FDA application NDA 205832. FDA, Silver Spring, MD.

FDA (2014k) Drug approval package: ORBACTIV (oritavancin). FDA application NDA 206334. FDA, Silver Spring, MD.

FDA (2014l) Drug approval package: OTEZLA (apremilast). FDA application NDA 205437. FDA, Silver Spring, MD.

FDA (2014m) Drug approval package: VIEKIRA PAK (ombitasvir, Paritaprevir, and Ritonavir co-packaged with dasabuvir). FDA application NDA 206619. FDA, Silver Spring, MD.

FDA (2014n) Drug approval package: ZONTIVITY (vorapaxar). FDA application NDA 204886. FDA, Silver Spring, MD.
FDA (2014o) Drug approval package: ZYDELIG (idelalisib). FDA application NDA 206545. FDA, Silver Spring, MD.

FDA (2014p) Drug approval package: ZYKADIA (ceritinib). FDA application NDA 205755. FDA, Silver Spring, MD.

FDA (2015a) Drug approval package: ADDYI (flibanserin). FDA application NDA 022526. FDA, Silver Spring, MD.

FDA (2015b) Drug approval package: ALECENSA (alectinib). FDA application NDA 208434. FDA, Silver Spring, MD.

FDA (2015c) Drug approval package: CORLANOR (ivabradine). FDA application NDA 206143. FDA, Silver Spring, MD.

FDA (2015d) Drug approval package: COTELLIC (cobimetinib). FDA application NDA 206192. FDA, Silver Spring, MD.

FDA (2015e) Drug approval package: CRESEMBA (isavuconazonium sulfate). FDA application NDA 207500. FDA, Silver Spring, MD.

FDA (2015f) Drug approval package: DAKLINZA (daclatasvir). FDA application NDA 206843. FDA, Silver Spring, MD.

FDA (2015g) Drug approval package: FARYDAK (panobinostat). FDA application NDA 207103. FDA, Silver Spring, MD.

FDA (2015h) Drug approval package: IBRANCE (palbociclib). FDA application NDA 207103. FDA, Silver Spring, MD.

FDA (2015i) Drug approval package: NINLARO (ixazomib citrate). FDA application NDA 208462. FDA, Silver Spring, MD.

FDA (2015j) Drug approval package: ODOMZO (sonidegib). FDA application NDA 205266. FDA, Silver Spring, MD.

FDA (2015k) Drug approval package: ORKAMBI (lumacaftor and ivacaftor). FDA application NDA 206038. FDA, Silver Spring, MD.
DMD # 78691

FDA (2015l) Drug approval package: REXULTI (brexpiprazole). FDA application NDA 205422. FDA, Silver Spring, MD.

FDA (2015m) Drug approval package: SAVAYSA (edoxaban). FDA application NDA 206316. FDA, Silver Spring, MD.

FDA (2015n) Drug approval package: UPTRAVI (selexipag). FDA application NDA 207947. FDA, Silver Spring, MD.

FDA (2015o) Drug approval package: VARUBI (rolapitant). FDA application NDA 206500. FDA, Silver Spring, MD.

FDA (2015p) Drug approval package: VIBERZI (eluxadoline). FDA application NDA 206940. FDA, Silver Spring, MD.

FDA (2015q) Drug approval package: VRAYLAR (cariprazine). FDA application NDA 204370. FDA, Silver Spring, MD.

FDA (2015r) Drug approval package: YONDELIS (trabectedin). FDA application NDA 207953. FDA, Silver Spring, MD.

FDA (2015s) Drug approval package: ZURAMPIC (lesinurad). FDA application NDA 207988. FDA, Silver Spring, MD.

FDA (2016a) Drug approval package: BRIVIACT (brivaracetam). FDA application NDA 205836. FDA, Silver Spring, MD.

FDA (2016b) Drug approval package: EPCLUSA (sofosbuvir and velpatasvir). FDA application NDA 208341. FDA, Silver Spring, MD.

FDA (2016c) Drug approval package: NUPLAZID (pimavanserin). FDA application NDA 207318. FDA, Silver Spring, MD.

FDA (2016d) Drug approval package: OCALIVA (obeticholic acid). FDA application NDA 207999. FDA, Silver Spring, MD.

FDA (2016e) Drug approval package: VENCLEXTA (venetoclax). FDA application NDA 208573. FDA, Silver Spring, MD.
FDA (2016f) Drug approval package: ZEPATIER (elbasvir and grazoprevir). FDA application NDA 208261. FDA, Silver Spring, MD.


Figure 1. Quantitation of new molecular entities (NMEs) acting as substrates in inhibition drug-drug interactions (DDIs) for drugs approved by the US FDA between 2013 and 2016 and quantitation of those DDIs. A) Therapeutic classes of NMEs acting as substrates in inhibition DDIs (N = 45 NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. B) Mechanisms of inhibition DDIs with NMEs acting as the substrate (N = 61 DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.

Figure 2. Quantitation of new molecular entities (NMEs) acting as substrates in induction drug-drug interactions (DDIs) for drugs approved by the US FDA between 2013 and 2016 and quantitation of those DDIs. A) Therapeutic classes of NMEs acting as substrates in induction DDIs (N = 46 NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. B) Mechanisms of induction DDIs with NMEs acting as the substrate (N = 51 DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.

Figure 3. Quantitation of new molecular entities (NMEs) acting as perpetrators in inhibition drug-drug interactions (DDIs) for drugs approved by the US FDA between 2013 and 2016 and quantitation of those DDIs. A) Therapeutic classes of NMEs acting as perpetrators in inhibition DDIs (N = 20 NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. B) Mechanisms of inhibition DDIs with NMEs acting as the perpetrator (N = 46 DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.

Figure 4. Quantitation of new molecular entities (NMEs) acting as perpetrators in induction drug-drug interactions (DDIs) for drugs approved by the US FDA between 2013 and 2016 and quantitation of those DDIs. A) Therapeutic classes of NMEs acting as perpetrators in induction DDIs (N = 7 NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. B) Mechanisms of induction DDIs with NMEs acting as the perpetrator (N = 10 DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.
Figure 5. Quantitation of new molecular entities (NMEs) acting as substrates of enzymes or transporters for drugs approved by the US FDA between 2013 and 2016. A) Drug-metabolizing enzymes contributing to NME metabolism. Only parent drugs as substrates of enzymes are shown. Other CYPs were not specified by the authors; other Phase II enzymes include SULT2A1, other sulfotransferases, glutathione S-transferases, and unspecified conjugated enzymes; others include catecholamine pathway enzymes, epoxide hydrolase, hydrolases, phospholipidase, phosphatase, proteinase, nucleases, nucleotidase, thymidine phosphorylase, and unspecified biotransformation enzymes. FMO, flavin-containing monooxygenase; AO, Aldehyde Oxidase. B) Transporters contributing to NME transport. Only parent drugs as substrates of transporters are shown.

Figure 6. Quantitation of new molecular entities (NMEs) acting as inhibitors of enzymes or transporters for drugs approved by the US FDA between 2013 and 2016. A) Drug-metabolizing enzymes inhibited by NMEs (open bars) and metabolites (closed bars). B) Transporters inhibited by NMEs (open bars) and metabolites (closed bars).

Figure 7. Quantitation of new molecular entities (NMEs) acting as inducers of enzymes for drugs approved by the US FDA between 2013 and 2016. Drug-metabolizing enzymes induced by NMEs (open bars) and metabolites (closed bars) are shown.
<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Inhibitor</th>
<th>Main Enzymes / Transporters Possibly Involved</th>
<th>AUC Ratio</th>
<th>Reference</th>
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<tr>
<td>Paritaprevir</td>
<td>Ritonavir</td>
<td>CYP3A, P-gp, BCRP, OATP1B1/3</td>
<td>47.43</td>
<td>(FDA, 2014m)</td>
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<td>Eliglustat</td>
<td>Ketoconazole/paroxetine</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;, CYP2D6</td>
<td>37.85 (PBPK in EMs)</td>
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<td>23.90</td>
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<td>Eliglustat</td>
<td>Fluconazole/terbinafine</td>
<td>CYP3A, CYP2D6</td>
<td>19.31</td>
<td>(AUC&lt;sub&gt;0-24h&lt;/sub&gt;, FDA, 2014c)</td>
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<td>Grazoprevir</td>
<td>Cyclosporine</td>
<td>OATP1B1/3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15.25 (AUC&lt;sub&gt;0-24h&lt;/sub&gt;)</td>
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<td>Lopinavir/ritonavir</td>
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<td>Grazoprevir</td>
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<td>10.22</td>
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<td>Eliglustat</td>
<td>Paroxetine</td>
<td>CYP2D6</td>
<td>10.00 (EMs)</td>
<td>(FDA, 2014c)</td>
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<td>Dasabuvir</td>
<td>Gemfibrozil</td>
<td>CYP2C8</td>
<td>9.90</td>
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<td>Eliglustat</td>
<td>Ketoconazole/paroxetine</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;, CYP2D6</td>
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<td>Ibrutinib</td>
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<td>Ivabradine</td>
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### Table

<table>
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<tr>
<th>Drug</th>
<th>Other Drug</th>
<th>Enzyme(s)</th>
<th>Value (Remarks)</th>
<th>Source</th>
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<tr>
<td>Eliglustat</td>
<td>Fluconazole</td>
<td>CYP3A</td>
<td>7.54 (PBPK in PMs)</td>
<td>FDA, 2014c</td>
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<td>Grazoprevir</td>
<td>Darunavir/ritonavir</td>
<td>CYP3A, OATP1B1/3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.49</td>
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<td>Simeprevir</td>
<td>Ritonavir</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.18</td>
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<td>Tasimelteon</td>
<td>Fluvoxamine</td>
<td>CYP1A2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.87</td>
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<td>Pirfenidone</td>
<td>Fluvoxamine</td>
<td>CYP1A2</td>
<td>6.81 (smokers), 3.97 (nonsmokers)</td>
<td>FDA, 2014d</td>
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<td>Itraconazole</td>
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<td>Simeprevir</td>
<td>Erythromycin</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.54</td>
<td>FDA, 2013i</td>
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<td>Flibanserin</td>
<td>Fluconazole</td>
<td>CYP3A, CYP2C19</td>
<td>6.41</td>
<td>FDA, 2015a</td>
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<tr>
<td>Venetoclax</td>
<td>Ketoconazole</td>
<td>CYP3A, P-gp</td>
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<td>Eliglustat</td>
<td>Ketoconazole</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.22 (PBPK in PMs)</td>
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<td>Ibrutinib</td>
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<td>sulfate (prodrug)</td>
<td>Butyrylcholinesterase</td>
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<td>Eliglustat</td>
<td>Paroxetine</td>
<td>CYP2D6</td>
<td>5.20 (IMs)</td>
<td>FDA, 2014c</td>
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</tbody>
</table>

Drugs were orally administered unless specified; IV, intravenously; EM, CYP2D6 extensive metabolizer; IM, CYP2D6 intermediate metabolizer; N/P – not provided; PM, CYP2D6 poor metabolizer; UM, CYP2D6 ultrarapid metabolizer

<sup>a</sup> – Also a substrate of P-gp based on in vitro results; inhibition of P-gp might contribute to the observed interaction

<sup>b</sup> – Also a substrate of P-gp and BCRP based on in vitro results

<sup>c</sup> – Also metabolized by CYP3A, CYP2C9, and CYP2C19; fluvoxamine inhibits these P450s
### TABLE 2. Induction DDIs with AUC ratios ≤ 0.2, NME as substrate

<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Main Enzymes /Transporters Possibly Involved</th>
<th>AUC Ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isavuconazonium sulfate</td>
<td>CYP3A, butyrylcholinesterase</td>
<td>0.03</td>
<td>(FDA, 2015e)</td>
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<td>Eliglustat</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.04 (PMs)</td>
<td>(FDA, 2014c)</td>
</tr>
<tr>
<td>Flibanserin</td>
<td>CYP3A, CYP2C19</td>
<td>0.04</td>
<td>(FDA, 2015a)</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.08 (PBPK)</td>
<td>(FDA, 2013g)</td>
</tr>
<tr>
<td>Eliglustat</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.09 (IMs)</td>
<td>(FDA, 2014c)</td>
</tr>
<tr>
<td>Eliglustat</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10 (EMs)</td>
<td>(FDA, 2014c)</td>
</tr>
<tr>
<td>Naloxegol</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.11</td>
<td>(FDA, 2014h)</td>
</tr>
<tr>
<td>Olaparib</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.11</td>
<td>(FDA, 2014g)</td>
</tr>
<tr>
<td>Rolapitant</td>
<td>CYP3A</td>
<td>0.12</td>
<td>(FDA, 2015o)</td>
</tr>
<tr>
<td>Suvorexant</td>
<td>CYP3A</td>
<td>0.12</td>
<td>(FDA, 2014b)</td>
</tr>
<tr>
<td>Tasimelteon</td>
<td>CYP3A&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.14</td>
<td>(FDA, 2014f)</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.15</td>
<td>(FDA, 2015h)</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>CYP3A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.17 (PBPK)</td>
<td>(FDA, 2015d)</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>CYP3A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.17</td>
<td>(FDA, 2016d)</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>CYP2B6, CYP2C8, CYP3A, P-gp, BCRP</td>
<td>0.19</td>
<td>(FDA, 2016b)</td>
</tr>
<tr>
<td>Netupitant</td>
<td>CYP3A</td>
<td>0.20</td>
<td>(FDA, 2014a)</td>
</tr>
</tbody>
</table>

Drugs were orally administered unless specified; in all the DDIs, rifampin was used as the inducer except for grazoprevir, where efavirenz was the inducer.

EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer

<sup>a</sup> Also a substrate of P-gp based on in vitro results; induction of P-gp might contribute to the observed interaction.

<sup>b</sup> Also metabolized by CYP1A2, CYP2C9, and CYP2C19; rifampin in an inducer of multiple P450s
Also a substrate of P-gp and BCRP based on in vitro results; induction of P-gp and BCRP might contribute to the observed interaction.
TABLE 3. Inhibition DDIs with AUC ratios ≥ 5, NME as inhibitor

<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Inhibitor</th>
<th>Main Enzymes / Transporters Possibly Involved</th>
<th>AUC Ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Ombitasvir, paritaprevir, and ritonavir</td>
<td>CYP3A, P-gp</td>
<td>85.92</td>
<td>(FDA, 2014m)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Paritaprevir, dasabuvir, and ritonavir</td>
<td>CYP3A, P-gp</td>
<td>78.68</td>
<td>(FDA, 2014m)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Ombitasvir, paritaprevir, dasabuvir, and ritonavir</td>
<td>CYP3A, P-gp</td>
<td>57.07</td>
<td>(FDA, 2014m)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Ombitasvir, paritaprevir, dasabuvir, and ritonavir</td>
<td>CYP3A, P-gp</td>
<td>5.78</td>
<td>(FDA, 2014m)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Idelalisib</td>
<td>CYP3A</td>
<td>5.15</td>
<td>(FDA, 2014o)</td>
</tr>
</tbody>
</table>

Drugs were orally administered unless specified.
TABLE 4. Induction DDIs with AUC ratios ≤ 0.5, NMEs as inducers

<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Inducer</th>
<th>Main Enzymes /Transporters</th>
<th>AUC Ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Ivacaftor and</td>
<td>CYP3A</td>
<td>0.18</td>
<td>(FDA, 2015k)</td>
</tr>
<tr>
<td></td>
<td>lumacaftor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivacaftor</td>
<td>Lumacaftor</td>
<td>CYP3A</td>
<td>0.20</td>
<td>(FDA, 2015k)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Dabrafenib</td>
<td>CYP3A</td>
<td>0.26</td>
<td>(FDA, 2013m)</td>
</tr>
</tbody>
</table>

Drugs were orally administered unless specified
Figure 1
Figure 2

A

![Bar chart showing the number of NMEs in different drug categories. The categories include Cancer treatments, Antivirals, CNS Agents, Cardiovascular drugs, Gastrointestinal agents, Metabolism disorder/endocrinology treatments, Respiratory Agents, Antifungals, and Musculoskeletal agents. The percentages of each category are 30%, 24%, 15%, 9%, 7%, 4%, 2%, 2%, 2%, 2%, 2% respectively.]

B

![Bar chart showing the number of DDIs associated with different enzymes and transporters. The enzymes and transporters include CYP3A, CYP3A and other P450s, P-gp, CYP3A and P-gp, CYP1A2, CYP2C8, CYP2C9, CYP2C19, UGT1A9 and UGT2B4, and CYP3A and other P450s/UGT/butyrylcholinesterase. The percentages of each category are 57%, 8%, 8%, 6%, 6%, 4%, 4%, 2%, 2%, 2%, 2% respectively.]

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Figure 3
Figure 4
Figure 5
Figure 6
Figure 7