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Title

Mechanisms and Clinical Significance of Pharmacokinetic-based Drug-drug Interactions with Drugs Approved by the U.S. Food and Drug Administration in 2017

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Running Title Page

a) Running title: A review of clinical DDIs in 2017 NDAs

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Number of words in the Discussion: 619

d) Abbreviations:

AUC, area under the time-plasma concentration curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; FDA, Food and Drug Administration; FDC, fixed-dose combination; MATE, Multi-antimicrobial extrusion protein; NTI, narrow therapeutic index; NDA, new drug application; NME, new molecular entity; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P450 or CYP, cytochrome P450; PBPK, physiologically-based pharmacokinetics, P-gp, P-glycoprotein; PGx, pharmacogenetic(s); PK, pharmacokinetic(s); PXR, pregnane X receptor; UGT, UDP-glucuronosyltransferase

Abstract

Pharmacokinetic-based drug-drug interaction (DDI) data for drugs approved by the U.S. Food and Drug Administration in 2017 (N = 34) were analyzed using the University of Washington Drug Interaction Database. The mechanisms and clinical relevance of these interactions were characterized based on information from new drug application reviews. CYP3A inhibition and induction explained a majority of the observed drug interactions (new drugs as victims or as perpetrators), and transporters mediated about half of all DDIs, alone or with enzymes. OATP1B1/1B3 played a significant role, mediating more than half of the drug interactions with AUC changes ≥ 5-fold. As victims, five new drugs were identified as sensitive substrates, namely abemeciclib, midostaurin, and neratinib for CYP3A, and glecaprevir and voxilaprevir for OATP1B1/1B3. As perpetrators, three drugs were considered strong inhibitors: ribociclib for CYP3A, glecaprevir/pibrentasvir for OATP1B1/1B3, and sofosbuvir/velpatasvir/voxilaprevir for OATP1B1/1B3 and BCRP. No strong inducer of enzymes or transporters was identified. DDIs with AUC changes ≥ 5-fold and almost all DDIs with AUC changes 2- to 5-fold had dose recommendations in their respective drug labels. A small fraction of DDIs with exposure changes < 2-fold had a labeling impact, mostly related to drugs with narrow therapeutic indices. As with drugs approved in recent years, all drugs found to be sensitive substrates or strong inhibitors of enzymes or transporters were among oncology or antiviral treatments, suggesting a serious risk of DDIs in these patient populations for whom therapeutic management is already complex due to poly-therapy.

Introduction

In the last few decades, the U.S. Food and Drug Administration (FDA) and the pharmaceutical industry have contributed to the development of a systematic, risk-based approach for evaluating pharmacokinetic (PK)-based drug-drug interactions (DDIs) and communicating the results to the scientific and medical communities. In the last two years, the approach recommended by the FDA has been updated (FDA , FDA 2017a, FDA 2017b, FDA 2018). These approaches are best expressed in New Drug Application (NDA) approval packages because they include pre-clinical and clinical investigational data of the new drugs and the implications of those findings in product labels. These NDA reviews are also useful because only a small portion of their data becomes available in the scientific literature, even at a later date. Thus, NDA reviews provide a unique perspective on the evolution of drug interaction science, acting like a snapshot of the implementation of DDI guidances and newer regulatory recommendations in the mechanistic and clinical contexts of various therapeutic classes. An example is how the complex metabolism-transporter interplay affects our evolving understanding of the mechanism and potential clinical risk associated with PK-based drug interactions of new drugs. In that context, this paper provides an analysis of the significant clinical DDIs associated with the 2017 NDAs and shows how to predict and manage possible DDI risk and to safely administer these new drugs in certain patient populations.

Methods

This analysis was performed using the University of Washington Metabolism and Transport Drug Interaction Database® (DIDB®) and the Pharmacogenetics (PGx) Database (e-PKGene®), (http://www.druginteractioninfo.org) following the methodology previously described (Yu et al. 2014, Yu et al. 2016, Yu et al. 2017, Yu et al. 2018). Clinical DDI study results were obtained from dedicated DDI clinical trials, PGx studies, as well as PBPK modeling studies that functioned as alternatives to dedicated clinical studies. Mean AUC ratios were the metric used to evaluate clinical studies, using AUC_{inf} unless otherwise noted. In the present analysis, all positive clinical studies, defined as AUC ratios ≥ 1.25 for inhibition DDIs or PGx studies and ≤ 0.8 for induction DDIs, were analyzed, including mechanistic and

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co-medication evaluations. To allow a general comparison for all DDIs included in this analysis, any drug interactions with AUC changes ≥ 5-fold, 2- to 5-fold, or 1.25- to 2-fold were considered strong, moderate, or weak inhibition or induction interactions, respectively, whether they are mediated by enzymes and/or transporters.

Results

A total of 34 NDAs (including one combination drug with two new molecular entities (NMEs), so total NME number = 35) were approved by the FDA in 2017, and their chemical structures are presented as supplemental data (Supplemental Table 1). The most represented therapeutic areas were oncology drugs (26%) and anti-infective agents (23%; including four antibacterials, three antivirals, and one antiparasitic), followed by central nervous system agents (12%) and metabolism disorder/endocrinology drugs (12%). This representation pattern of therapeutic classes is similar to that observed with drugs approved from 2013 to 2016 (Yu et al. 2018). Among the nine new chemical entities approved for cancer treatment, seven were kinase inhibitors, suggesting that this therapeutic class has a predominant role as a cancer treatment target.

All the NDAs had in vitro and/or clinical drug metabolism and transport interaction data. Among them, 26 NDAs had clinical drug interaction data available, five presented PGx information, and six had PBPK simulation data. There were approximately 150 clinical DDIs with positive results, including 61 inhibition DDIs (plus two PGx studies) and 29 induction interaction studies where NMEs served as substrates and 54 inhibition interaction studies and three induction DDIs where NMEs served as perpetrators. Given the large amount of information included in the NDA reviews, only the most significant DDIs with exposure changes ≥ 5-fold will be highlighted in detail in the following sections and presented in Table 1, while the rest of drug interaction data will be briefly reviewed.

NMEs as Substrates of Enzymes

All 35 NMEs were assessed in vitro as substrates of specific drug-metabolizing enzymes. The numbers of NME substrates of drug-metabolizing enzymes are presented in Figure 1A. As expected, CYP3A played a major role, metabolizing 2/3 of the NMEs, followed by CYP2D6, CYP1A2, and the CYP2C families.

Not surprisingly, all inhibition DDIs with AUC ratios ≥ 5 (N = 3 NMEs) were mediated by CYP3A under co-administration with ketoconazole, the standard strong CYP3A inhibitor (Table 1). Due to the large increases in drug exposure, labeling recommendations (avoidance, dose reduction, considering alternative therapies and monitoring adverse reactions) were included regarding concomitant use with strong CYP3A inhibitors. Based on the FDA classification, abemaciclib, midostaurin, and neratinib were considered sensitive substrates of CYP3A. These three drugs are kinase inhibitors indicated for the treatment of breast cancer (abemaciclib and neratinib) or leukemia (midostaurin), suggesting a need to carefully manage drug use when these patients are also treated with CYP3A inhibitors.

Abemaciclib exhibited the largest exposure change, with up to a 16-fold increase predicted using PBPK modeling and simulations in healthy subjects upon co-administration with ketoconazole at a dose expected to produce 100% inhibition of CYP3A (FDA 2017p). In vitro studies suggest that abemaciclib is primarily metabolized by CYP3A to several active metabolites. Because these metabolites are equipotent to the parent drug, the total analyte exposure (including abemaciclib and these active metabolites) and the relative potency-adjusted unbound exposure of abemaciclib plus these active metabolites were also used as markers of drug exposure by the sponsor. With ketoconazole, the total analyte AUC was predicted to increase 6.87-fold and the potency-adjusted unbound AUC was increased 2.87-fold. A smaller change in the exposure was predicted or observed with co-administration of other strong CYP3A inhibitors. For example, itraconazole (dose to assume 90% CYP3A inhibition) was predicted to increase abemaciclib AUC 7.15-fold, the total analyte AUC 2.76-fold, and the relative potency-adjusted unbound AUC of abemaciclib plus its active metabolites 2.20-fold in healthy subjects using PBPK models. In a clinical study in which patients were administered clarithromycin 500 mg twice daily for 14 days, there was a 3.37-fold increase in abemaciclib AUC, a 2.19-fold in total analyte AUC, and a 1.70-fold increase in the

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relative potency-adjusted unbound AUC of abemaciclib plus its active metabolites. The differential effects of ketoconazole on the PK of abemaciclib in comparison with other strong CYP3A inhibitors may be due to several factors including the non-linearity of the AUC vs I/K_i relationship between 90% and 100% inhibition (Ito et al. 2004) and/or the differential effects of strong inhibitors on first-pass versus systemic CYP3A metabolism of abemaciclib (Boxenbaum 1999). A similar behavior has been observed with midazolam, the sensitive substrate of CYP3A, where co-administration with ketoconazole (400 mg once daily for 5 days) increased midazolam AUC approximately 17-fold (Boulenc et al. 2016), while itraconazole (200 mg once daily for 4 days) and clarithromycin (500 mg twice daily for 7 days) resulted in a relatively smaller increase (10.80- and 8.39-fold increase, respectively) (Olkkola et al. 1994, Gurley et al. 2006). Given the large magnitude of exposure change in abemaciclib when co-administered with ketoconazole and the potential concerns for unknown off-target toxicities related to increased abemaciclib exposure, concomitant use of ketoconazole with abemaciclib should be avoided. For other strong CYP3A inhibitors, a reduction of abemaciblib dose is recommended upon concomitant administration (FDA 2017p). With the moderate inhibitors diltiazem and verapamil, the increase in the exposure of abemaciclib and in the relative potency-adjusted unbound AUC of abemaciclib plus its active metabolites were both predicted to be low and not considered clinically meaningful.

Midostaurin undergoes extensive metabolism, primarily by CYP3A to two active metabolites, CPG52541 and CPG62221. Concomitant administration of ketoconazole (400 mg once daily for 10 days) with a 50 mg single dose of midostaurin in healthy subjects increased the AUC of midostaurin and CGP62221 10.42- and 3.51-fold, respectively, and increased the $AUC_{0\text{-}120h}$ of CGP52421 1.21-fold (AUC_{inf} of CGP52421 was not evaluated due to the its long elimination half-life of 482 h) (Dutreix et al. 2013, FDA 2017m). Interestingly, when multiple doses of midostaurin (50 or 100 mg twice daily for 28 days) were co-administered with itraconazole (100 mg twice daily for 13 doses) in patients, on Day 28 the AUC_{tau} of midostaurin and CGP52421 was only increased 1.63- and 1.20-fold, respectively, and the AUC_{tau} of CGP62221 decreased by 13%. The C_{min} value on Day 28 for midostaurin, CGP62221, and CGP52421

was increased 2.1-, 1.2-, and 1.3-fold, respectively. Of note, midostaurin exhibited time-dependent PK with an initial increase in C_{min} reaching its highest value during the first week, followed by a decline to a steady state after approximately 28 days of administration. The PK of CGP62221 showed a similar behavior, while the plasma concentrations of CGP52421 continued to increase after one month of treatment. According to the sponsor, this is possibly due to auto-induction of CYP3A as in vitro studies showed that both midostaurin and the two metabolites had the potential to induce CYP3A at clinically relevant concentrations (FDA 2017m). The PK profile of midostaurin explains why the effect of strong CYP3A inhibitors on the PK of midostaurin appears to be dependent on the duration of midostaurin dosing, with a 10-fold increase in exposure observed after a single dose administration of midostaurin and a 2-fold increase observed at steady state. Since midostaurin is used at multiple doses in cancer patients, and considering the 2-fold increase observed in midostaurin exposure at steady state, monitoring for increased risk of adverse reactions is recommended in the label when co-administered with strong CYP3A inhibitors (FDA 2017m).

Finally, for neratinib, a 5-fold increase in AUC was observed when it was co-administered with ketoconazole (400 mg once daily for 5 days) in healthy subjects (FDA 2017k). The potential drug interaction risk with less potent CYP3A inhibitors was not investigated, but based on the result with ketoconazole, the label recommends that concomitant use of neratinib with both strong and moderate CYP3A inhibitors should be avoided. The sponsor was required to conduct a post-marketing evaluation (PBPK modeling/simulation or a clinical PK trial) of the effect of moderate CYP3A inhibitors on the PK of neratinib and its active metabolites.

Compared to inhibition results, more drugs were sensitive to induction with AUC changes ≥ 5-fold (N = 8 NMEs) with some drug exposures almost completely abolished by concomitant administration with the strong inducer rifampin (Table 1). Here also, drugs for cancer treatment are predominant, and six of them are kinase inhibitors. All the induction interactions with AUC changes ≥ 5-fold were also mediated by CYP3A under co-administration with rifampin or carbamazepine. As expected, abemaciclib, midostaurin,

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and neratinib, found to be sensitive to inhibition, were also sensitive to induction, with drug exposures significantly reduced by 90-95% upon co-administration with rifampin (600 mg once daily for 8 or 14 days). Consequently, concomitant administration of these drugs with strong CYP3A inducers should be avoided (FDA 2017k, FDA 2017m, FDA 2017p). In addition, similar changes in drug exposure (80-95% decrease) were observed or predicted for the following five drugs: acalabrutinib, brigatinib, deflazacort, naldemedine, and ribociclib, and the same labeling recommendations were included for concomitant use with strong CYP3A inducers (FDA 2017c, FDA 2017f, FDA 2017g, FDA 2017i, FDA 2017o). In vitro studies suggest that all eight drugs are mainly eliminated by hepatic metabolism, primarily by CYP3A. Except midostaurin, they are also substrates of P-glycoprotein (P-gp), and brigatinib is also metabolized by CYP2C8 (FDA 2017c, FDA 2017f, FDA 2017g, FDA 2017i, FDA 2017k, FDA 2017m, FDA 2017o, FDA 2017p). Therefore, it is possible that multiple mechanisms were involved in the induction interactions by rifampin and carbamazepine.

CYP3A played a predominant role in these significant inhibition and induction interactions. Specifically, out of 12 sensitive substrates of P450s, eight drugs (67%) were found to be sensitive substrates of CYP3A (AUC ratios $\geq$ 5 in the presence of strong CYP3A inhibitors), and CYP3A was involved in all the induction interactions with AUC ratios $\leq$ 0.2 (Yu et al. 2018).

For inhibition DDIs with AUC ratios of 1.25-5 (35 DDIs with 12 NMEs involved), most of the interactions happened with the above eight NMEs when co-administered with CYP3A inhibitors with different potencies. In addition, valbenazine showed a 2-fold increase in both parent and its active metabolite alpha-dihydrotetrabenzine upon co-administration with ketoconazole, suggesting that it is a moderate sensitive substrate of CYP3A (FDA 2017h). Among the 35 DDIs, only two interactions were not mediated by CYP3A, with CYP2D6 and UDP-glucuronosyltransferase (UGT) 1A9/2B7 involved in the interactions with deutetrabenazine and ertugliflozin, respectively. Deutetrabenazine was identified as a moderate sensitive substrate of CYP2D6, with approximately a 3-fold increase in the exposure of the total active metabolites alpha- and beta-deutetrabenazine when co-administered with paroxetine, a strong

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CYP2D6 inhibitor (FDA 2017d). This result is consistent with pharmacogenetic studies where it was found that the total alpha- and beta-deutetrabenazine exposure in subjects with impaired CYP2D6 function (poor metabolizers) was 2-fold higher than that in subjects with functional CYP2D6 (intermediate and extensive metabolizers). For ertugliflozin, in vitro studies showed that it is metabolized by UGT1A9 and UGT2B7. PBPK models predicted a 1.51-fold increase in its exposure when co-administered with mefenamic acid, a UGT inhibitor. However, a pooled analysis of ertugliflozin AUC values from 417 subjects showed that the impact of UGT1A9 allelic variants on AUC were within 90-110% of the wild type and were not considered clinically relevant (FDA 2017n). As expected, almost all the DDIs with AUC ratios of 2-5 triggered dose recommendations in the labels, such as avoidance, dose reduction, and monitoring for adverse reactions, whereas for DDIs with exposure changes less than 2-fold, only about half of the interactions had a labeling impact like dose reduction or monitoring for potential adverse reactions.

NMEs as Inhibitors of Enzymes

Following the 2012 FDA DDI guidance recommendations for in vitro evaluation, 32 parent drugs and 24 metabolites (including the active moieties of three prodrugs) were tested for their inhibition potential on drug-metabolizing enzymes. The numbers of NMEs with positive results are presented in Figure 1B. The largest number of drugs were inhibitors of CYP3A (N = 16), followed by CYP2C9, CYP1A2, CYP2C8, CYP2D6, CYP2C19, and CYP2B6.

Clinically, there were approximately 40 DDIs involving five drugs (NMEs = 6, with one combination of 2 NMEs) with AUC ratios $\geq$ 1.25, including three antivirals, one cancer treatment agent, and one central nervous system agent. Ribociclib (breast cancer treatment) was the only strong inhibitor (Table 1). In vitro, ribociclib showed reversible ($K_{i,u}$ = 30.0 µM) and mechanism-based inhibition ($K_{I,u}$ = 4.44 µM, k_{inact} = 0.02 /min) of CYP3A. Based on the basic model (FDA 2012), ribociclib was predicted to inhibit CYP3A at clinically relevant concentrations (C_{max} = 4 µM at 600 mg once daily in cancer patients). Indeed, according to PBPK models, ribociclib was predicted to increase midazolam AUC 5.17-fold at

clinical doses of 600 mg once daily for 8 days, suggesting that it is a strong inhibitor of CYP3A. In agreement with that prediction, when ribociclib was administered to healthy subjects at a lower dose of 400 mg once daily for 8 days, a 3.89-fold increase in midazolam AUC was observed. Based on these results, caution is recommended in the label when ribociclib is co-administered with CYP3A substrates with narrow therapeutic indices (NTI). Also, the dose of a sensitive CYP3A substrate may need to be reduced (FDA 2017i).

CYP3A was also the primary enzyme mediating moderate and weak enzyme inhibitions (37 DDIs with five drugs involved), and only a few DDIs were mediated by CYP2C8, CYP1A2, and UGT1A1 individually or in combination with other enzymes or transporters. Based on the FDA classification, several drugs were identified as moderate or weak inhibitors of P450s through evaluations with index substrates. For example, letermovir was shown to be a moderate inhibitor of CYP3A (midazolam AUC ratio = 3.44), and glecaprevir/pibrentasvir and safinamide were weak inhibitors of CYP1A2 (caffeine AUC ratios of 1.35 and 1.30, respectively). Of note, about 20% of inhibition interactions could be attributed to inhibition of both enzymes and transporters, some mainly mediated by enzymes and some mainly by transporters. However, the complex interplay between enzymes and transporters makes it challenging to determine the exact contribution of each mechanism. All DDIs with AUC changes of 2- to 5-fold triggered labeling recommendations, such as dose reduction, monitoring, or caution. In contrast, among all the DDIs with AUC changes less than 2-fold, only the interactions of letermovir with repaglinide or rosiglitazone (both antidiabetic agents), predicted using PBPK models, were considered clinically meaningful and it was recommended to closely monitor glucose plasma concentrations upon co-administration (FDA 2017l).

NMEs as Inducers of Enzymes

The induction potential of most NMEs on drug-metabolizing enzymes was systemically evaluated in vitro using human hepatocytes. A total of 31 parent drugs and 15 metabolites were assessed for their induction potential of P450s and phase II enzymes (glutathione S-transferases, Sulfotransferases, and UGTs).

Regulation of pregnane X receptor (PXR) was investigated for a few drugs. The numbers of NMEs with positive induction results are presented in Figure 1C. Comparable numbers of drugs were found to be inducers of CYP3A (N = 10), CYP2B6 (N =10) and CYP1A2 (N = 9). Most of the induction effects however were observed at drug concentrations far higher than the drug's C_{max} values and based on predictions using basic or mechanistic models, these effects were not considered to be clinically relevant, and therefore no clinical studies were warranted. In addition, some drugs exhibited both induction and inhibition toward the same P450 in vitro. For example, letermovir induced CYP2B6 at concentrations up to 20 µM (mRNA expression: 1.0- to 2.4-fold and 1-8% of positive control; activity: 2.4- to 2.7-fold and 29-65% of positive control), while weak inhibition of CYP2B6 was also observed in vitro (IC_{50} = 54 µM). Therefore, the overall impact on CYP2B6 was expected to be minimal.

Only three drugs showed in vivo induction of enzymes, with two DDIs possibly mediated by CYP3A (telotristat ethyl and safinamide) and one by CYP2C9/2C19 (letermovir). No drug behaved as a strong clinical inducer. The largest effect was induction of CYP3A by telotristat ethyl (prodrug), with a 51% decrease observed in midazolam AUC. Although no in vitro induction of CYP3A mRNA expression was observed with telotristat ethyl concentrations of 3 and 10 µM, a concentration-dependent increase in PXR activation by telotristat ethyl (5.3-fold and 17.8% of the positive control rifampin at 50 µM) and telotristat (6.5-fold and 23.1% of the positive control rifampin at 50 µM) was observed. Induction of UGTs might also be involved as the exposure to the active metabolite 1'-hydroxymidazolam similarly decreased by 49%, possibly due to increased glucuronidation of 1'-hydroxymidazolam by UGTs. However, in vitro induction of UGTs by telotristat ethyl was not evaluated and such studies have been requested as a post-marketing commitment (FDA 2017s). The second largest induction was caused by letermovir, decreasing the AUC of voriconazole by 44%. According to the sponsor, the induction was attributable to CYP2C9 and/or CYP2C19. However, no induction of CYP2C19 mRNA expression or activity was observed at letermovir concentrations up to 1.75 µM (of note, this test concentration is far below C_{max}, which is 23 and 50 µM after oral and IV dosing of letermovir, respectively), and the induction potential of letermovir

on CYP2C9 was not evaluated in vitro. These clinical study results suggest that concomitant use of telotristat ethyl or letermovir may decrease the efficacy of drugs that are substrates of CYP3A or CYP2C9/2C19 by decreasing their systemic exposure by approximately 50%, respectively. Therefore, it was recommended to monitor the plasma concentrations of victim drugs that are substrates of these enzymes and adjust their dosages if necessary (FDA 2017l, FDA 2017s).

NMEs as Substrates of Transporters

Twenty-seven NMEs and 14 metabolites were evaluated in vitro as substrates of a total of 17 transporters, and 19 parent drugs and 6 metabolites were found to be substrates of nine transporters (Figure 2A). The largest number of drugs were found to be substrates of P-gp (N = 18), followed by breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, and OATP1B3.

There were approximately 20 clinical DDI studies with AUC ratios ≥ 1.25 (with five drugs involved) mainly mediated by transporters, namely OATP1B1, OATP1B3, P-gp, and BCRP. OATP1B1/1B3 played a dominant role, mediating more than half of these DDIs, some with involvement of P-gp and BCRP. As discussed in the enzyme section, almost all the moderate sensitive and sensitive substrates of CYP3A are also substrates of P-gp and, to avoid redundancy, these interactions are not included in this section. Among the five drugs (NMEs = 6 including one combination drug with two NMEs) involved, three drugs (NMEs = 4) are antivirals. Approximately 80% of the DDIs were from two drugs, glecaprevir/pilbentasvir and voxilaprevir, both indicated for the treatment of hepatitis C virus (HCV) infection. About half of the interactions were co-medication studies due to the complex polypharmacy in this patient population.

Five drug interaction studies (involving two NMEs) had AUC changes greater than 5-fold, all mediated by OATP1B1/1B3, with partial contributions from P-gp and BCRP for some of those interactions (Table 1). Based on these inhibition study results, two NMEs, namely glecaprevir and voxilaprevir, were identified as sensitive substrates of OATP1B1/1B3. Co-administration of voxilaprevir in healthy subjects with cyclosporine (600 mg oral single dose), an inhibitor of OATP1B1/1B3 (also of other transporters), significantly increased voxilaprevir AUC approximately 10-fold. Similarly, a 600 mg single dose oral

administration of rifampin in healthy subjects resulted in an 8-fold increase in voxilaprevir AUC, suggesting strong inhibition of OATP1B1/1B3. There was some in vitro evidence suggesting uptake transporters involvement in the transport of voxilaprevir in hepatocytes, although specific transporters were not identified. Voxilaprevir is also a substrate of P-gp and BCRP, with efflux ratios of 6.5 and 3.9, respectively, in transporter-transfected MDCK II cells (FDA 2017q). Therefore, the higher change in voxilaprevir AUC observed with cyclosporine may involve inhibition of P-gp and BCRP as cyclosporine is also an inhibitor of these two transporters. Regarding glecaprevir, its exposure was increased 8.55- and 5.08-fold in healthy subjects under co-administration with a single oral dose of rifampin (600 mg) or cyclosporine (400 mg), respectively. As voxilaprevir, glecaprevir is a substrate of OATP1B1 (K_m = 0.098 μM), OATP1B3 (K_m = 0.19 μM), P-gp (efflux ratio = 7.8), and BCRP (efflux ratio = 9.3) (FDA 2017j). As expected based on the clinical findings, concomitant administration of glecaprevir or voxilaprevir with OATP inhibitors is contraindicated or not recommended (FDA 2017j, FDA 2017q).

For DDIs with AUC changes 1.25- to 5-fold, OATP1B1/1B3 was also primarily involved, mediating 2/3 of the interactions. For example, the interactions between the combination drug glecaprevir/pibrentasvir and some commonly prescribed co-medications such as atazanavir/ritonavir, cobicistat, darunavir/ritonavir, and lopinavir/ritonavir were mainly mediated by OATP1B1/1B3, with possible involvement of P-gp and/or BCRP. Although inhibition of P-gp seems to contribute to all the drug interactions with AUC ratios of 1.25-5, it was the main driving mechanism in only three DDIs involving two NMEs: (i) co-administration of betrixaban with verapamil and ketoconazole showed a 3.06- and 2.12-fold increases in the exposure of betrixaban; (ii) naldemedine AUC was increased 1.79-fold when it was co-administered with cyclosporine. Based on these results, it is recommended to reduce the dose of betrixaban or monitor for potential naldemedine-related adverse reactions when they are co-administered with P-gp inhibitors (FDA 2017e, FDA 2017o).

On the other hand, several drugs seemed more sensitive to induction than inhibition. For example, when the combination drug glecaprevir/pibrentasvir was co-administered with multiple oral doses of rifampin

(600 mg once daily for 17 days), the AUC and C_{max} values of glecaprevir and pibrentasvir were significantly reduced by approximately 90%, mainly due to induction of P-gp (induction of CYP3A might also contribute to the reduction in glecaprevir exposure since, in vitro, glecaprevir exhibited some metabolism, primarily by CYP3A). The less potent inducers carbamazepine and efavirenz decreased these drugs' exposure by 50-70% and 50%, respectively. Consequently, considering the potential risk of therapeutic failure, co-administration of glecaprevir/pibrentasvir is contraindicated with rifampin, while not recommended with carbamazepine or efavirenz (FDA 2017j).

NMEs as Inhibitors of Transporters

In vitro, the inhibition potential of NMEs and their metabolites was assessed towards 19 transporters. A total of 31 NMEs and 26 metabolites (including the active moieties of two prodrugs) were evaluated, with 25 NMEs and 9 metabolites showing inhibition. The largest number of drugs was found to be inhibitors of BCRP (N = 17), followed by P-gp (N = 15), OATP1B1 (N = 8), and OATP1B3 (N = 8) (Figure 2B).

Clinically, there were over 20 DDIs involving six drugs (NMEs = 7, including one combination drug with two NMEs) with AUC ratios ≥ 1.25, with about 1/3 of the interactions mediated by both transporters and enzymes. Among these inhibitors, there are three antivirals, two cancer treatment agents, and one central nervous system agent. Even though OATP1B1 and OATP1B3 were not the main transporters inhibited in vitro, they played a dominant role in vivo, mediating half of the drug interactions including all the strong interactions (2 DDIs; Table 1) and most of the moderate ones (6 out of 9 DDIs).

Two drugs, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, both HCV combination drugs, exhibited strong inhibition of OATP1B1/1B3 and/or BCRP, with greater than 5-fold increase in the exposure of victim drugs atorvastatin or rosuvastatin (Table 1). Co-administration with glecaprevir/pibrentasvir (300 mg/120 mg once daily for 10 days) in healthy subjects significantly increased the AUC and Cmax of atorvastatin, a clinical substrate of OATP1B1/1B3, 8.28- and 22-fold, respectively. In vitro, glecaprevir inhibited OATP1B1 (IC_{50} = 0.017 μM) and OATP1B3 (IC_{50} = 0.064 μM), and pibrentasvir inhibited OATP1B1 (IC_{50} = 1.3 μM with 4% BSA), but not OATP1B3 (IC_{50} > 30

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μM). Of note, glecaprevir also weakly inhibited CYP3A in vitro (IC_{50} = 28.4 μM) and atorvastatin is a moderate sensitive substrate of CYP3, therefore inhibition of CYP3A might also contribute to the overall effect. Considering the large increase in atorvastatin exposure, co-administration of glecaprevir/pibrentasvir with atorvastatin is not recommended (FDA 2017j). The drug interaction risks with other statins (lovastatin, pravastatin, rosuvastatin, simvastatin) were evaluated as well. Exposures to these statins were increased to a much smaller extent (1.70- to 2.32-fold) in healthy subjects upon co-administration with gelcaprevir/pibrentasvir. However, there was a higher increase (4.10- to 4.50-fold) in the active metabolites lovastatin hydroxyl acid and simvastatin acid. Therefore, co-administration of lovastatin or simvastatin with glecaprevir/pibrentasvir is also not recommended, while dose reduction is recommended for pravastatin and rosuvastatin (FDA 2017j).

The other strong inhibition was caused by the combination drug sofosbuvir/velpatasvir/voxilaprevir (400 mg/100 mg/100 mg + 100 mg voxilaprevir once daily for 15 days; voxilaprevir as an NME), with 7.35- and 17.96-fold increases in the AUC and C_{max} of co-administered rosuvastatin, respectively, a clinical substrate of BCRP, OATP1B1, and OATP1B3 (FDA). In vitro studies showed that voxilaprevir is an inhibitor of OATP1B1 (IC_{50} = 0.18 μM) and OATP1B3 (IC_{50} = 0.70 μM), and velpatasvir inhibits BCRP, OATP1B1, and OATP1B3 with IC_{50} values of 0.30, 1.5, and 0.26 μM, respectively. Sofosbuvir only weakly inhibited BCRP (35% inhibition at 100 μM) and OATP1B3 (IC_{50} = 203.5 μM). Based on in vitro to in vivo prediction calculations (FDA 2012), both velpatasvir and voxilaprevir were likely to inhibit these transporters at clinically relevant concentrations. In vivo, co-administration of velpatasvir (100 mg QD for 11 days) increased pravastatin AUC 1.35-fold, likely due to inhibition of hepatic OATPs (Mogalian et al. 2016, FDA 2017q). A larger effect was observed for rosuvastatin, with approximately a 2.8-fold increase in its AUC following co-administration of velpatasvir (100 mg QD for 11 days), due to the inhibition of both OATPs and BCRP (Mogalian et al. 2016, FDA 2017q). Therefore, the significant increase in rosuvastatin under co-administration with sofosbuvir/velpatasvir/voxilaprevir may be

attributable to the combined inhibition of BCRP, OATP1B1, and OATP1B3 by velpatasvir and voxilaprevir.

P-gp was involved in approximately 1/3 of the clinical interactions, with most victim exposure changes less than 2-fold. The largest effect mediated by P-gp was observed with the combination drug sofosbuvir/velpatasvir/voxilaprevir, increasing dabigatran (clinical substrate of P-gp) AUC 2.59-fold. Clinical monitoring of dabigatran is recommended when co-administered with this combination drug (FDA 2017q). Although the exposure increases of the P-gp substrate digoxin were lower (1.30-1.48) when co-administered with glecaprevir/pibrentasvir, neratinib, or valbenazine, these effects were considered clinically relevant and monitoring or dose reduction was recommended in the drugs' labels when used concomitantly with P-gp substrates with a NTI such as digoxin (FDA 2017h, FDA 2017j, FDA 2017k). Regarding other transporters, abemaciclib was found to be a weak inhibitor of multi-antimicrobial extrusion protein (MATE) 1, MATE2-K, and organic cation transporter (OCT) 2, as it slightly increased metformin (clinical substrate of these transporters) AUC 1.37-fold. However, this effect was not considered clinically relevant. Similar to enzyme-mediated DDIs, almost all the interactions with AUC ratios of 2-5 triggered dose recommendations, while for DDIs with AUC ratios less than 2, the majority were not considered clinically meaningful.

In vitro-to-in vivo Predictions

Following recommendations of the 2012 FDA DDI guidance, in vitro-to-in vivo predictions were performed using both basic and mechanistic models. PBPK models were used to predict the risk of drug interactions for six drugs and the predicted results were used to support specific label recommendations (Table 2). Among them, five drugs (abemaciclib, acalabrutinib, deflazacort, naldemedine, and ribociclib) are substrates of CYP3A. Typically, the drug interaction risk with one strong inhibitor or inducer was evaluated using a clinical study, while the risks with other strong inhibitors or inducers or less potent inhibitors or inducers were predicted using PBPK models. PBPK models were also used to predict the inhibition potential of different dosing regimen for ribociclib. The effect of ribociclib at 400 mg once

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daily for 8 days on CYP3A was investigated in a clinical trial in healthy subjects using midazolam as the probe substrate, while the recommended dose of 600 mg once daily for 8 days was assessed using PBPK models. As expected, a larger increase in midazolam was predicted with the higher dose of ribociclib and label recommendations were based on those predictions (FDA 2017i).

Basic model predictions were performed more widely for all drugs. In general, good predictions were observed for drugs that showed high inhibition or induction potency in vitro, such as ribociclib (C_{max} = 4 µM), which showed reversible ($K_{i,u}$ = 30.0 µM) and mechanism-based inhibition ($K_{I,u}$ = 4.44 µM, k_{inact} = 0.02 /min) of CYP3A; glecaprevir (C_{max} = 0.712 µM), which inhibited P-gp (IC_{50} = 0.33 µM), BCRP (IC_{50} = 2.3 µM), OATP1B1 (IC_{50} = 0.017 µM), and OATP1B3 (IC_{50} = 0.064 µM); letermovir (C_{max} = 22.7 µM (oral), 49.6 µM (IV)), which inhibited OATP1B1 (IC_{50} = 2.9 µM) and OATP1B3 (IC_{50} = 1.1 µM) (FDA 2017i, FDA 2017j, FDA 2017l). Indeed, in vivo, all these drugs exhibited moderate to strong inhibition of the relevant enzyme or transporter. However, there were several cases where in vitro findings did not accurately predict the clinical results using basic models. For example, betrixaban, letermovir, and telotristat ethyl all showed inhibition of P-gp in vitro. Based on the [I]/IC_{50} ratios, betrixaban and telotristat ethyl were expected to inhibit P-gp at the gut level, while letermovir had the potential to cause both systemic and intestinal inhibition of P-gp. However, when evaluated in vivo, there was no significant increase in the exposure of the co-administered P-gp substrates digoxin or fexofenadine (AUC ratios 0.90-1.14), indicating no clinical inhibition of P-gp (FDA 2017e, FDA 2017l, FDA 2017s). On the other hand, several drugs that were predicted to have a remote risk of drug interaction showed positive clinical inhibition. For instance, for the combination drug glecaprevir/pibrentasvir, glecaprevir only weakly inhibited CYP3A4 (IC_{50} = 28.3 µM) but not CYP1A2, and pibrentasvir did not inhibit any P450s. Based on the R_1 value of 1.05 (assuming competitive inhibition, K_i = 14.15 µM; C_{max} = 0.712 µM) for CYP3A4, glecaprevir was not likely to inhibit this enzyme at clinically relevant concentrations. However, in a cocktail study the combination exhibited weak inhibition of both CYP1A2 and CYP3A, with a 35% and 27% increase observed in the AUC of

caffeine and midazolam, respectively (FDA 2017j). Similarly, safinamide showed reversible (IC_{50} = 47.7 μM; K_i = 54 μM, competitive) and mechanism-based inhibition (K_I = 33.5 μM, K_{inact} = 0.075/min) of CYP1A2, and its metabolite NW-1153 also showed weak inhibition of CYP1A2 (36% inhibition under pre-incubation and 8.9% inhibition under co-incubation). With both R_1 and R_2 values < 1.1, no clinical inhibition of CYP1A2 was expected. However, safinamide co-administration caused a 30% increase in caffeine AUC, suggesting weak inhibition of CYP1A2 in vivo (FDA 2017r). Although the slight increases in the exposure to these probes were not considered clinically meaningful by the sponsors, based on the current FDA classification, both drugs are still considered weak inhibitors. If only the basic models were used and no clinical studies had been performed, these weak inhibitions would not have been identified. One possible reason causing the prediction discrepancy of these basic models may be due to the failure to consider the drug's protein or plasma binding capacity. Of note, for the transporters P-gp, BCRP, and OATP1B1/1B3, among the 13 drugs with prediction values higher than the cut-offs, nine drugs were highly bound to plasma (bound > 96%). In the most recent FDA guidance (2017), the prediction methods and cut-offs have been revised and it is now recommended to use unbound inhibition parameters and free plasma concentrations in the calculations. Also, a pre-incubation condition is recommended for transporter inhibition studies. However, because the unbound inhibition parameters were not available for most of the drugs approved in 2017, it was not possible to evaluate if prediction accuracy would have been enhanced with the new regulatory framework.

Discussion and Conclusions

PK-based DDI data from NDA reviews for drugs approved by the FDA in 2017 were thoroughly reviewed and the clinical significance of the results was assessed. As expected, CYP3A mediated the majority of interactions, whether NMEs serving as substrates or as perpetrators. A total of 11 drugs were found to be clinical substrates of CYP3A, with AUC increases ≥ 25% when co-administered with a strong CYP3A inhibitor (clarithromycin, itraconazole, ketoconazole, ritonavir, or voriconazole). Among them, nine (82%) were also substrates of P-gp in vitro, consistent with previous findings and confirming the

significant overlap between substrates of CYP3A and P-gp (Christians et al. 2005, Zhou 2008, Yu et al. 2018). Inhibition of OATP1B1/1B3 also played a substantial role. All large interactions with AUC changes of the victim drug equal to or greater than 5-fold were mediated by either CYP3A or OATP1B/1B3, with contributions from other transporters such as P-gp and/or BCRP. Five drugs were considered sensitive substrates, including abemeciclib, midostaurin, and neratinib for CYP3A, and glecaprevir and voxilaprevir for OATP1B1/1B3. When NMEs were evaluated as perpetrators, three drugs were considered strong inhibitors, including ribociclib for CYP3A, glecaprevir/pibrentasvir for OATP1B1/1B3, and sofosbuvir/velpatasvir/voxilaprevir for OATP1B1/1B3 and BCRP. No strong inducer was identified.

As noted in previous evaluations (Yu et al. 2018), transporters are playing an increasing role in clinical drug interactions. This is mostly explained by an improved ability to detect transporter-mediated DDIs because of a better understanding of their role in drug disposition as well as deliberate efforts to shift molecular structures away from P450-mediated interactions during early phase of drug discovery (Hughes et al. 2011, Cheng et al. 2007). For the 2017 NMEs, they mediated about half of all drug interactions, as main or partial contributors to the overall effect, with often complex interplays observed between several transporters, or between transporters and enzymes, particularly for DDIs involving antiviral combination drugs. Two combination drugs, glecaprevir/pibrentasvir and sofosbuvri/velpatasvir/voxilaprevir, were identified as both sensitive substrates and strong inhibitors of transporters. Despite our improved knowledge of DDI underlying mechanisms, because of the complexity of the enzyme-transporter interplay, understanding the true contribution of a transporter in a given interaction remains challenging due to the lack of specific transporter substrates and inhibitors. Also, it is often difficult to generalize transporter-based DDIs among substrates and inhibitors.

In terms of labeling impact, all large DDIs with exposure changes equal to or greater than 5-fold triggered labeling recommendations such as contraindication, not recommended, or avoidance of concomitant administration. Almost all drug interactions with AUC changes of 2- to 5-fold also had some language in

the labels recommending dose adjustment of the victim drug or monitoring for adverse reactions or plasma concentrations. However, for DDIs with exposure changes of less than 2-fold, there were differences in labeling impact depending on the NME's role in the drug interaction. When NMEs were victims, approximately half of the drug interactions had some language in the label like dose adjustment or monitoring, while only about 20% of DDIs triggered labeling recommendations when NMEs were the perpetrators. In both cases, labeling recommendations were mainly related to NTI drugs. Interestingly, almost all induction DDIs with AUC changes less than 5-fold (NMEs as substrates) had labeling language to avoid co-administration with inducers given the impact of possible loss of efficacy for these classes of drugs.

Finally, it is worthy to note that, as observed in previous years, the largest clinical interactions involving NMEs identified as sensitive substrates and strong inhibitors were observed with oncology or HCV drugs, including four (out of the nine approved) oncology drugs and two (out of three approved) antiviral drugs. This suggests a significant risk of clinically significant DDIs in these patient populations for whom therapeutic management is already complex due to poly-therapy.

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Authorship Contributions

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Footnotes

Table 1.

BID, twice daily; N/P, not provided; NTI, narrow therapeutic index; QD, once daily; SD, single dose

[a] All drugs were administered orally under fasting conditions unless otherwise specified.

[b] alone on Day 1 of Period 1 then 1 day after rifampin pretreatment (Day 18 of period 2)

[c] alone on Day 1 of Period 1 then 1 day after rifampin pretreatment (Day 18 of period 2)

[d] alone on Day 1 of Period 1 then with rifampin on Day 14 of Period 2

Table 2.

NTI, narrow therapeutic index

[a] The effect of a moderate inducer on the pharmacokinetics of abemaciclib was requested as a post-market requirement via PBPK models or clinical trials

[b] midazolam was administered as 400 mg once daily for 8 days

[c] midazolam was administered as 600 mg (recommended clinical dose) once daily for 8 days

Legends for Figures

Figure 1. The numbers of NMEs (open bars) and metabolites (closed bars) of substrates (A), inhibitors (B), or inducers (C) of drug-metabolizing enzymes. The nuclear receptor PXR is also included for induction assessment (C). ACE2, angiotensin-converting enzyme 2; ALDH2, aldehyde dehydrogenase 2; FMO, flavin-containing monooxygenase; GST, glutathione S-transferase; MAO, monoamine oxidase; SULT, sulfotransferase.

Figure 2. The numbers of NMEs (open bars) and metabolites (closed bars) of substrates (A) or inhibitors (B) of drug transporters. BSEP, bile salt export pump; OAT, organic anion transporter; MRP, multidrug resistance-associated protein.

Table 1. Drug interactions with AUC changes ≥ 5

Victim Drug	Victim Drug Dosing Regimen [a]	Perpetrator	Perpetrator Dosing Regimen [a]	Population/Study Design	AUC Ratio	C_{max} Ratio	Enzyme/Transporters Possibly Involved	Labeling Impact	Reference
Inhibition DDIs, NMEs as substrates									
abemaciclib	50 or 200 mg SD	ketoconazole	dose to assume 100% CYP3A inhibition	healthy subjects/PBPK modeling	15.73	N/P	CYP3A (P-gp)	avoided with ketoconazole	(FDA 2017p)
midostaurin	50 mg SD	ketoconazole	400 mg QD for 10 days	healthy subjects/parallel, placebo-controlled	10.42, 3.51 (CGP62221), 1.21 (CGP52421)	1.83	CYP3A4	monitor for increased risk of adverse reactions and consider alternative therapies	(FDA 2017m)

voxilaprevir	100 mg SD	cyclosporine	600 mg SD	healthy subjects/random crossover	9.73	14.29	OATP1B1, OATP1B3, P-gp, BCRP	not recommended with OATP inhibitors	(FDA 2017q)
glecaprevir	glecaprevir/pibrentasvir 300 mg/120 mg SD	rifampin	600 mg SD	healthy subjects/one sequence	8.55	6.52	OATP1B1, OATP1B3	(contraindication with rifampin due to induction)	(FDA 2017j)
voxilaprevir	100 mg SD	rifampin	600 mg SD	healthy subjects/random crossover	7.96	8.74	OATP1B1, OATP1B3	contraindicated with rifampin	(FDA 2017q)
abemaciclib	50 or 200 mg SD	itraconazole	dose to assume 90% CYP3A inhibition	healthy subjects/PBPK modeling	7.15, 2.20 (abemaciclib, M2, M18, and	N/P	CYP3A (P-gp)	dose reduction with strong CYP3A inhibitors (except ketoconazole)	(FDA 2017p)

					M20)				
glecaprevir	glecaprevir/pibrentasvir 300 mg/120 mg QD for 21 days	atazanavir/ritonavir	300 mg/100 mg QD for 14 days	healthy subjects/one sequence	6.53	4.51	OATP1B1, OATP1B3 (P-gp, BCRP)	contraindicated with atazanavir and not recommended with ritonavir	(FDA 2017j)
glecaprevir	glecaprevir/pibrentasvir 300 mg/120 mg SD	cyclosporine	400 mg SD	healthy subjects/one sequence	5.08	4.51	OATP1B1, OATP1B3, P-gp, and BCRP	not recommended with cyclosporine in subjects requiring stable cyclosporine doses > 100 mg per day	(FDA 2017j)
neratinib	240 mg SD	ketoconazole	400 mg QD for 5 days	healthy subjects/random crossover	5.16	3.63	CYP3A4 (P-gp)	avoided with strong or moderate CYP3A inhibitors	(FDA 2017k), (Abbas et al. 2011)
Induction DDIs, NMEs as substrates									

abemaciclib	200 mg SD	rifampin	600 mg QD for 14 days	healthy subjects/one sequence	0.05, 0.35, 1.31, 0.20 (abemaciclib, M2, M18, and M20)	0.08, 0.96, 4.26, 0.64 (abemaciclib, M2, M18, and M20)	CYP3A (P-gp)	avoided with strong CYP3A inducers	(FDA 2017p)
deflazacort	18 mg SD	rifampin	600 mg QD for 10days	not provided/not provided	0.06 (21-desacetyl deflazacort)	0.08	CYP3A4 (P-gp)	avoided with strong or moderate CYP3A4 inducers	(FDA 2017g)
midostaurin	50 mg SD	rifampin	600 mg QD for 14	healthy	0.06	0.63	CYP3A4	avoided with strong	(Dutreix

			days	subjects/parallel, placebo-controlled	(CGP62221), 0.41 (CGP52421)	(CGP62221), 0.65 (CGP52421)		CYP3A4 inducers	et al. 2013, FDA 2017m)
neratinib	240 mg SD with a standard meal	rifampin	600 mg QD for 8 days	healthy subjects/one sequence	0.12	0.23	CYP3A4 (P-gp)	avoided with strong or moderate CYP3A4 inducers	(FDA 2017k)
glecaprevir	glecaprevir/pibrentasvir 300/120 mg SD [b]	rifampin	600 mg QD for 17 days	healthy subjects/one sequence	0.12	0.14	P-gp (CYP3A)	contraindicated with rifampin	(FDA 2017j)
ribociclib	600 mg SD	rifampin	600 mg QD for 14 days	healthy subjects/one sequence	0.11	0.19	CYP3A (P-gp)	avoided with strong CYP3A inducers and consider alternative therapies	(FDA 2017i)

pibrentasvir	glecaprevir/pibrentasvir 300/120 mg SD [c]	rifampin	600 mg QD for 17 days	healthy subjects/one sequence	0.13	0.17	P-gp	contraindicated with rifampin	(FDA 2017j)
acalabrutinib	100 mg BID	rifampin	600 mg QD	healthy subjects/PBPK modeling	0.17 (acalabrutinib), 0.39 (ACP-5862)	N/P	CYP3A (P-gp)	avoided with strong CYP3A inducers; if not, increase acalabrutinib dose	(FDA 2017f)
naldemedine	0.2 mg SD	rifampin	600 mg daily for 17 days	healthy subjects/one sequence	0.17 (naldemedine), 2.45 (nornaldemedine)	0.61 (naldemedine), 3.17 (nornaldemedine)	CYP3A4 (P-gp)	avoided with strong CYP3A4 inducers	(FDA 2017o)

pibrentasvir	glecaprevir/pibrentasvir 300/120 mg SD [d]	rifampin	600 mg QD for 17 days	healthy subjects/one sequence	0.17	0.21	P-gp	contraindicated with rifampin	(FDA 2017j)
brigatinib	180 mg SD	rifampin	600 mg daily for 7 days	healthy subjects/one sequence	0.20	0.40	CYP3A, CYP2C8 (P-gp)	avoided with strong CYP3A inducers	(FDA 2017c)
abemaciblib	200 mg SD	carbamazepine	400 mg BID for 24 days	healthy subjects/PBPK modeling	0.20	N/P	CYP3A (P-gp)	avoided with strong CYP3A inducers	(FDA 2017p)
Inhibition DDIs, NMEs as inhibitors									
glecaprevir/pibrentasvir	glecaprevir/pibrentasvir 300/120 mg QD 10 days	atorvastatin	10 mg QD for 14 days	healthy subjects/one sequence	8.28	22.00	OATP1B1, OATP1B3 (CYP3A)	not recommended with atorvastatin	(FDA 2017j)
voxilaprevir	sofosbuvir/velpatasvir/voxilaprevir + voxilaprevir 400 mg/100 mg/100	rosuvastatin	10 mg SD	healthy subjects/one sequence	7.35	17.96	BCRP, OATP1B1, OATP1B3	not recommended with BCRP substrates	(FDA 2017q)

	mg + 100 mg QD with food QD for 15 days								
ribociclib	600 mg QD for 8 days	midazolam	5 mg SD	healthy subjects/PBPK modeling	5.17	2.41	CYP3A	caution or dose reduction with CYP3A substrates with an NTI	(FDA 2017i)

Table 2. PBPK modeling and simulation results used to support label recommendations

Drug Name	Inhibition Study (AUC Ratio)	Labeling Impact	Induction Study (AUC Ratio)	Labeling Impact	Reference
As substrate					
abemaciclib [a]	Clarithromycin (3.37) - clinical	dose reduction with strong CYP3A inhibitors (except ketoconazole)	rifampin (0.05) - clinical	avoided with strong CYP3A inducers	(FDA 2017p)
	Ketoconazole (15.73) - PBPK	avoided with ketoconazole	carbamazepine (0.20) - PBPK	avoided with strong CYP3A inducers	
	Itraconazole (7.15) - PBPK	dose reduction with strong CYP3A inhibitors (except ketoconazole)			
	Diltiazem (3.95) - PBPK	none			
	Verapamil (2.28) - PBPK	none			
acalabrutinib	Itraconazole (4.96) - clinical	avoided with strong CYP3A inhibitors; if inhibitor is used, use of acalabrutinib	rifampin (0.21) - clinical	avoided with strong CYP3A inducers; if not, dose increased to 200 mg BID	(FDA 2017f)

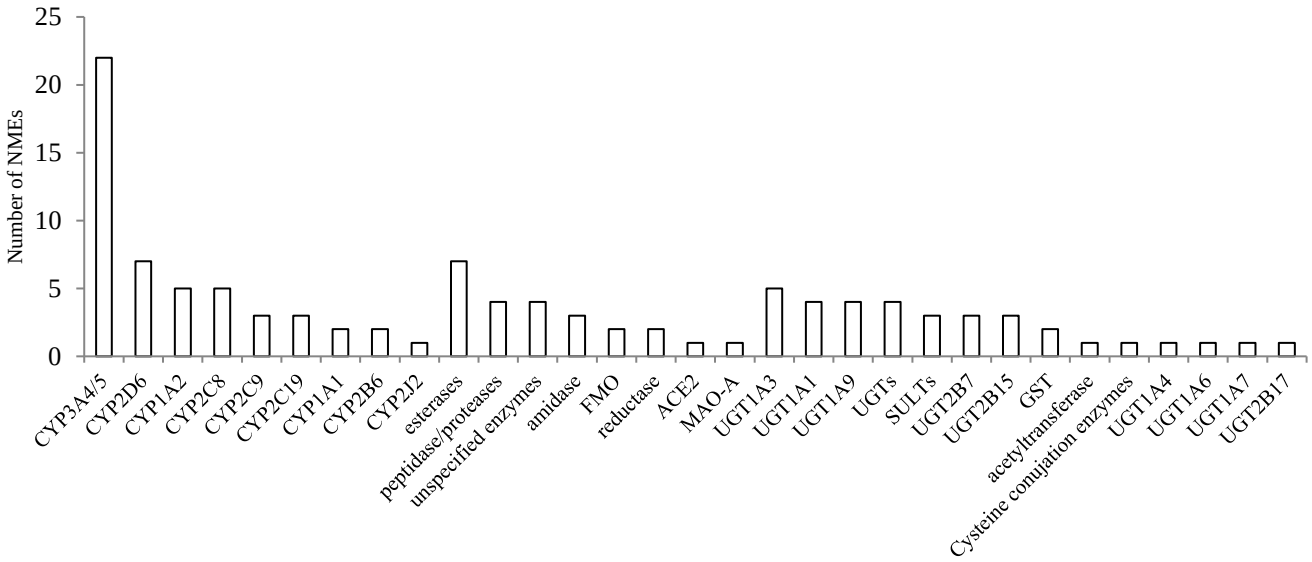
		should be interrupted			
	Clarithromycin (3.34) - PBPK	avoided with strong CYP3A inhibitors; if inhibitor is used, use of acalabrutinib should be interrupted	carbamazepine (0.39) - PBPK	avoided with strong CYP3A inducers; if not, dose increased to 200 mg BID	
	Erythromycin (2.76) - PBPK	dose reduction to 100 mg QD	efavirenz (0.39) - PBPK	none	
	Diltiazem (2.28) - PBPK	dose reduction to 100 mg QD			
	Fluconazole (2.43) - PBPK	dose reduction to 100 mg QD			
	Fluvoxamine (1.37) - PBPK	none			
deflazacort	clarithromycin (3.38) - clinical	dose reduction to 1/3 of the recommended dose with strong CYP3A inhibitors	rifampin (0.06) - clinical	avoided with strong CYP3A inducers	(FDA 2017g)

	fluconazole (3.97) - PBPK	dose reduction to 1/3 of the recommended dose with moderate CYP3A inhibitors	efavirenz (0.29) - PBPK	avoided with moderate CYP3A inducers	
naldemedine	itraconazole (2.92) - clinical	monitoring for potential naldemedine-related adverse reactions with strong CYP3A inhibitors	rifampin (0.17) - clinical	avoided with strong CYP3A inducers	(FDA 2017o)
	fluconazole (1.90) - PBPK	monitoring for potential naldemedine-related adverse reactions with moderate CYP3A inhibitors	efavirenz (0.57) - PBPK	the clinical consequence with moderate CYP3A inducer is unknown	
ribociclib	ritonavir (3.21) - clinical	avoided with strong CYP3A inhibitors; if not, dose reduction to 400 mg QD	rifampin (0.11) - clinical	avoided with strong CYP3A inducers	(FDA 2017i)
	ketoconazole (3.09) - PBPK	avoided with strong CYP3A inhibitors; if not, dose reduction to 400 mg QD	carbamazepine (0.48) - PBPK	avoided with strong CYP3A inducers	
	itraconazole (2.69) - PBPK	avoided with strong CYP3A inhibitors; if not, dose reduction to 400 mg QD	efavirenz (0.40) - PBPK	none	
	erythromycin (1.93) -	avoided with strong CYP3A inhibitors;			

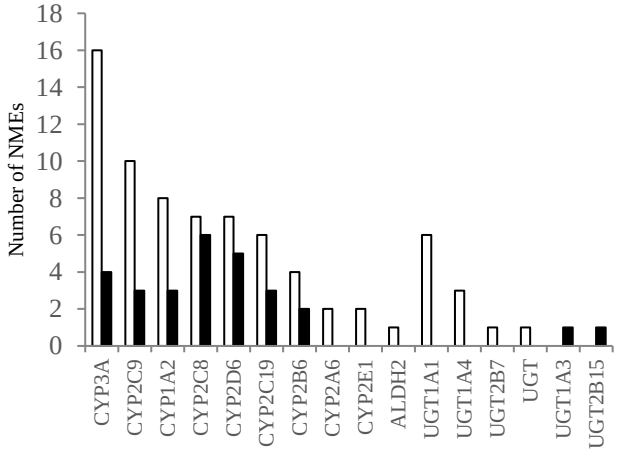
	PBPK	if not, dose reduction to 400 mg QD			
	fluvoxamine (1.02) - PBPK	none			
ertugliflozin	mefenamic acid (1.51) - PBPK	none	rifampin (0.61) - clinical	none	(FDA 2017n)
As inhibitor					
ribociclib	midazolam [b] (3.89) - clinical	caution with or reduce dose of CYP3A substrates with a NTI	Not applicable	Not applicable	(FDA 2017i)
	midazolam [c] (5.17) - PBPK	caution with or reduce dose of CYP3A substrates with a NTI			

Figure 1.

A.



B.



C.

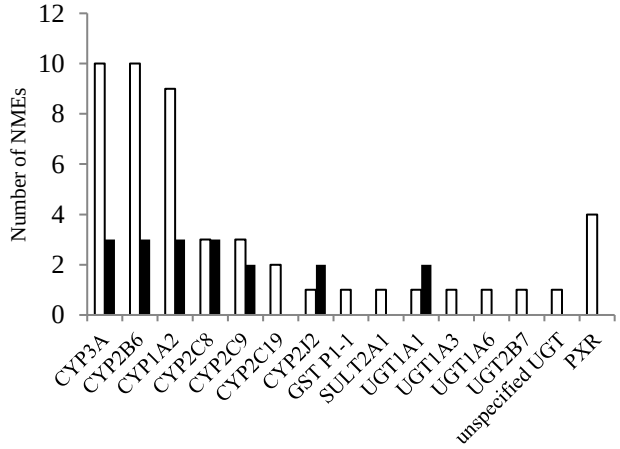
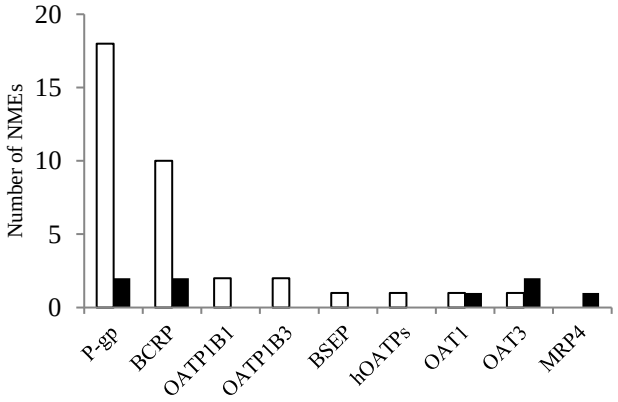


Figure 2.

A.



B.