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

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ABSTRACT

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

Introduction

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

A total of 33 NDAs were approved by the FDA and are summarized in Table 1, with the chemical structures presented in Supplemental Table 1. The most represented therapeutic areas were oncology drugs (30%), followed by cardiovascular drugs, central nervous system agents, and anti-infective agents, with four drugs approved (12%) in each class. All of the NDAs had drug metabolism and/or transporter data available and therefore are fully analyzed in this review. Among them, 22 (67%) were evaluated in patients with various degrees of organ impairment, eight (24%) presented PGx information, and seven (21%) had physiologically based PK (PBPK) simulation data. Of note, six NMEs were administered as prodrugs (namely, aripiprazole lauroxil, isavuconazonium sulfate, ixazomib citrate, saquinavir, tenofovir alafenamide sulfate, and uridine triacetate), with their respective metabolites (aripiprazole, isavuconazole, ixazomib, LBQ657, tenofovir, and uridine) being pharmacologically
TABLE 1
NDAs approved by the FDA in 2015 (ordered by approval date)

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>DDI</th>
<th>HI/RI</th>
<th>PBPK</th>
<th>PGx</th>
<th>Therapeutic Class</th>
<th>Approval Date</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Cardiovascular drugs</td>
<td>January 8</td>
<td>FDA (2015w)</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Cancer treatments</td>
<td>February 3</td>
<td>FDA (2015n)</td>
</tr>
<tr>
<td>Lenzatinib</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cancer treatments</td>
<td>February 13</td>
<td>FDA (2015q)</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Cancer treatments</td>
<td>February 23</td>
<td>FDA (2015i)</td>
</tr>
<tr>
<td>Ceftazidime (and avibactam)</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Anti-infective agents</td>
<td>February 25</td>
<td>FDA (2015d)</td>
</tr>
<tr>
<td>Isavuconazonium sulfate</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Anti-infective agents</td>
<td>March 6</td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td>Cholic acid</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Metabolism disorder/endocrinology treatments</td>
<td>March 17</td>
<td>FDA (2015f)</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cardiovascular drugs</td>
<td>April 15</td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Deoxycholic acid</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Metabolism disorder/endocrinology treatments</td>
<td>April 29</td>
<td>FDA (2015p)</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Gastrointestinal agents</td>
<td>May 27</td>
<td>FDA (2015zc)</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cardiovascular drugs</td>
<td>June 22</td>
<td>FDA (2015o)</td>
</tr>
<tr>
<td>Lumacaftor (and ivacaftor)</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Respiratory system agents</td>
<td>July 2</td>
<td>FDA (2015u)</td>
</tr>
<tr>
<td>Sacubitril (and valsaltr)</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Cardiovascular drugs</td>
<td>July 7</td>
<td>FDA (2015k)</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Central nervous system agents</td>
<td>July 10</td>
<td>FDA (2015v)</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cancer treatments</td>
<td>July 24</td>
<td>FDA (2015t)</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Anti-infective agents</td>
<td>July 24</td>
<td>FDA (2015j)</td>
</tr>
<tr>
<td>Filbanserin</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Central nervous system agents</td>
<td>August 18</td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>Rolapitant</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Antimetecine</td>
<td>September 1</td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>Urine triacetate</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Metabolism disorder/endocrinology treatments</td>
<td>September 4</td>
<td>FDA (2015ze)</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>Y*</td>
<td>Central nervous system agents</td>
<td>September 17</td>
<td>FDA (2015zd)</td>
</tr>
<tr>
<td>Trifluridine (and tipiracil)</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Cancer treatments</td>
<td>September 22</td>
<td>FDA (2015r)</td>
</tr>
<tr>
<td>Insulin degradate</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Hormones</td>
<td>September 25</td>
<td>FDA (2015y)</td>
</tr>
<tr>
<td>Aripiprazole lauroxil</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Central nervous system agents</td>
<td>October 5</td>
<td>FDA (2015c)</td>
</tr>
<tr>
<td>Patiromer</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Antidotest</td>
<td>October 21</td>
<td>FDA (2015zh)</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Cancer treatments</td>
<td>October 23</td>
<td>FDA (2015zf)</td>
</tr>
<tr>
<td>Elvitegravir, cobicistat, emtricitabine</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Anti-infective agents</td>
<td>November 5</td>
<td>FDA (2015m)</td>
</tr>
<tr>
<td>(and tenofovir alafenamide fumarate sulfate)</td>
<td>Y</td>
<td>Y*</td>
<td>Y</td>
<td>N</td>
<td>Anti-infective agents</td>
<td>November 10</td>
<td>FDA (2015h)</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cancer treatments</td>
<td>November 13</td>
<td>FDA (2015x)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Y*</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Cancer treatments</td>
<td>November 20</td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td>Ixazomib citrate</td>
<td>Y</td>
<td>Y*</td>
<td>N</td>
<td>N</td>
<td>Cancer treatments</td>
<td>November 12</td>
<td>FDA (2015b)</td>
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<tr>
<td>Alectinib</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cancer treatments</td>
<td>December 11</td>
<td>FDA (2015b)</td>
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<tr>
<td>Trabectedin</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cancer treatments</td>
<td>November 21</td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td>Lenisurdin</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Antigout and uricosuric agents</td>
<td>November 22</td>
<td>FDA (2015g)</td>
</tr>
</tbody>
</table>

N, studies not included in the NDA reviews; Y, studies included in the NDA reviews.

*Only population PK data are available for both HI and RI, and therefore are not included in this analysis.

*Only population PK data are available for RI, and therefore are not included in this analysis.

*Predrug.

*Only preclinical data are presented.

*Only population PK data are available for HI, and therefore are not included in this analysis.

*Only population PK data are available for HI, and are not included in this analysis; clinical data are available only for HI.

**PBPK modeling and simulations were used to support historical PK data under different clinical situations for DDIs, but were not used to recommend dosage.

*Population PK data are presented for mild HI and mild/moderate RI; others are from clinical data.

active. However, only three of the active metabolites are newly approved chemical entities (isavuconazole, ixazomib, and sacubitrit metabolite LBQ657) and are presented in this review. Finally, five NDAs described combination drugs: ACYCAZ (ceftazidime and avibactam), ENTRESTO (sacubitrit and valsaltrant), GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate), LONSURF (trifluridine and tipiracil), and ORKAMBI (lumacaftor and ivacaftor), in which only avibactam, lumacaftor, savubitril, tenofovir alafenamide fumarate, and tipiracil are NMEs and are discussed in this review.

Metabolism and Enzyme-Mediated DDIs

Thirty NMEs approved in 2015 were evaluated in vitro as substrates, inhibitors, and/or inducers of clinically important DMEs. When considered as substrates, 27 NMEs were shown to be metabolized by at least one enzyme, with the majority primarily metabolized by one or more cytochrome P450 (P450) (Fig. 1A; Table 2). As expected, and similar to approvals from the previous two years (Yu et al., 2014, 2016), CYP3A4/5 was shown to metabolize the largest number of NMEs in vitro, although not necessarily as the major enzyme. In vivo studies further confirmed that 12 of these NMEs were indeed clinical CYP3A substrates, with systemic exposure increases \( \geq 25\% \) when coadministered with the strong CYP3A inhibitors itraconazole (200 mg orally once daily), ketocoxazole (200 orally once or twice daily or 400 mg orally once daily), or posaconazole (400 mg orally twice daily), resulting in the following maximum area under the curve (AUC) and \( C_{\text{max}} \) ratios (in decreasing order of magnitude): ivabradine, 7.70 and 3.60; cobimetinib, 6.70 and 3.20; isavuconazole (the active metabolite of prodrug isavuconazonium sulfate), 5.22 and 1.09; flibanserin, 4.61 and 1.84; cariprazine, 3.78 and 3.26; daclatasvir, 3.00 and 1.57; sonidegib, 2.26 and 1.50; brexpiprazole, 2.17 and 1.18; palbociclib, 1.85 and 1.35; alectinib, 1.75 and 1.18; panobinostat, 1.70 and 1.60; and trabectedin, 1.66 and 1.22, respectively. Of note, six of these NMEs are also substrates of P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) (Table 2), and inhibition of those transporters may also contribute to the observed increased exposure (details of which are reviewed in the subsequent transporter section). Based on the FDA classification, ivabradine, cobimetinib, and isavuconazole can be considered sensitive substrates of CYP3A, with AUC ratios \( \geq 5 \) in the presence of strong CYP3A inhibitors; the significant changes in exposure suggesting a primary role of CYP3A in the disposition of these drugs (\( \text{fra}_{\text{CYP3A}} \geq 0.8 \)). Based on these results, concomitant use of strong CYP3A inhibitors with ivabradine (FDA, 2015g) and...
isavuconazonium sulfate (FDA, 2015i) is contraindicated, and should be avoided with cobimetinib (FDA, 2015h). Coadministration of the moderate CYP3A inhibitors diltiazem (120 mg orally twice daily), verapamil (120 mg orally twice daily), and grapefruit juice (dosing regimen unavailable) resulted in a 2- to 3-fold increase in ivabradine AUC and $C_{\text{max}}$ and a 20%–60% increase in its active metabolite, S18982, exposure. On the basis of these results, concomitant use of moderate CYP3A inhibitors with ivabradine should be avoided (FDA, 2015g). For cobimetinib, the interactions with less potent CYP3A inhibitors were studied using PBPK simulations. It was predicted that the exposure of cobimetinib to any significant extent. According to the product label, concomitant use of moderate CYP3A inhibitors with cobimetinib should be avoided. If avoiding concurrent use is not possible, a dose reduction of cobimetinib could be considered (FDA, 2015h).

For isavuconazonium sulfate, coadministration of lopinavir/ritonavir (400 mg/100 mg orally twice daily), which are both CYP3A strong inhibitors, increased the exposure to isavuconazole by approximately 2-fold, and caution is recommended when isavuconazonium sulfate is coadministered with lopinavir/ritonavir with monitoring for the signs of isavuconazole toxicity (FDA, 2015i). For the remaining nine drugs with 1.25 $\leq$ AUC ratios < 5 in the presence of a strong CYP3A inhibitor, concomitant use with strong CYP3A inhibitors is either contraindicated (filbanserin), to be avoided (palbociclib, sonidegib, and trabectedin), or dose reduction should be considered (brexpiprazole (FDA, 2015v), cariprazine (FDA, 2015d), daclatasvir (FDA, 2015j), and panobinostat (FDA, 2015l)), according to the drugs’ respective product labels; however, no dose adjustment is recommended for patients taking strong CYP3A inhibitors with alectinib since the effect of posaconazole on alectinib exposure (AUC ratio = 1.75) was not considered clinically meaningful by the sponsor (FDA, 2015b). As expected, most of these drugs (except cariprazine, which was not evaluated with strong inducers) were also sensitive to induction by rifampin (600 mg orally once daily) or St. John’s Wort extract (300 mg orally three times daily), yielding labeling recommendations for all of them (with the exception of alectinib) when coadministered with strong inducers of CYP3A.

Based on preclinical studies, other P450 isoforms (namely, CYP2D6, CYP2C8, CYP2C19, CYP2C9, and CYP2B6) were also involved in the metabolism of six, four, four, three, and two NMEs, respectively (Fig. 1A). However, contributions from these enzymes to the drugs’ overall disposition were considered limited, and no drugs were identified as sensitive substrates of any of these enzymes based on the follow-up clinical studies. The highest AUC change was observed with brexipiprazole, with a 2-fold increase in CYP2D6 extensive metabolizers (EMs) when coadministered with quinidine (324 mg orally once daily), a strong CYP2D6 inhibitor. Similarly, the brexipiprazole AUC increased to the same level after coadministration of ketoconazole (200 mg orally twice daily), a strong CYP3A inhibitor, indicating possible equal contribution of both CYP3A and CYP2D6 to the drug’s metabolism. Additionally, several NMEs were found to be primarily metabolized by non-P450 enzymes: edoxaban and selepxip, which are mainly metabolized by hepatic carboxysterase 1 with minor contributions from P450 enzymes (except cariprazine, which was not evaluated with strong inducers) labeling recommendations for all of them (with the exception of alectinib) when coadministered with strong inducers of CYP3A.

When NMEs were considered as perpetrators, 29 were investigated in vitro for the potential to inhibit DMEs. Twenty-one NMEs were found by the sponsor (FDA, 2015b) to be potent inhibitors of DMEs (open bars) and metabolites (filled bars). Other phase II enzymes include SULT2A1, other sulfotransferases, glutathione S-transferases, and unspecified conjugation enzymes; others include epoxide hydrolase, nucleotidase, thymidine phosphorylase, and unspecified biotransformation enzymes.

**Fig. 1.** Quantitation of compounds acting as substrates (NMEs) or inhibitors (NMEs and metabolites) of DMEs in vitro. (A) Phase I and II enzymes contributing to NME metabolism. (B) DMEs inhibited by NMEs (open bars) and metabolites (filled bars). (C) DMEs induced by NMEs (open bars) and metabolites (filled bars). Other phase II enzymes include SULT2A1, other sulfotransferases, glutathione S-transferases, and unspecified conjugation enzymes; others include epoxide hydrolase, nucleotidase, thymidine phosphorylase, and unspecified biotransformation enzymes.
TABLE 2
Enzymes and transporters involved in the NDA elimination pathways

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Main Elimination Route</th>
<th>Enzyme Involved</th>
<th>Transporter Involved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>Minimal metabolism, 62% in the urine and 35% in the feces (primarily as parent in both)</td>
<td>Carboxylesterase 1, phase II conjugation, CYP3A</td>
<td>P-gp, OATP1B1</td>
<td>FDA (2015w)</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Metabolism, 74.1% in the feces and 17.5% in the urine (percentage of parent versus metabolites not available)</td>
<td>CYP3A, SULT2A1</td>
<td>P-gp, BCRP</td>
<td>FDA (2015n)</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Metabolism, 64% in the feces and 25% in the urine (parent &lt;2.5% overall in both)</td>
<td>Aldehyde oxidase, CYP3A4, other P450s (not specified), phase II enzymes like GSH conjugation and other biotransformation</td>
<td>P-gp, BCRP</td>
<td>FDA (2015q)</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Metabolism, 29%–51% in the urine (parent &lt;2.5%) and 44%–77% in the feces (parent &lt;3.5%),</td>
<td>CYP3A, CYP2D6, 2C19, UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B4</td>
<td>P-gp</td>
<td>FDA (2015i)</td>
</tr>
<tr>
<td>Cefazidime (and avibactam)</td>
<td>Not metabolized in the liver, renal excretion, 97% in the urine (80%–90% as parent)</td>
<td>None</td>
<td>OAT1, OAT3</td>
<td>FDA (2015d)</td>
</tr>
<tr>
<td>Isavuconazonium sulfate</td>
<td>Metabolism, 46% in the feces and 46% in the urine (active isavuconazole &lt;1%)</td>
<td>Esterases, CYP3A4, CYP3A5, UGTs</td>
<td>None</td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Cholic acid</td>
<td>Joins the endogenous bile acid pool in the enterohepatic circulation mainly in conjugated forms; any cholic acid not absorbed will be excreted in the feces alone or as deoxycholic acid</td>
<td>CYP3A4, UGT2A1 and UGT2A2</td>
<td>BSEP, BCRP</td>
<td>Deo and Bandiera (2008); Blazquez et al. (2012); Perreault et al. (2013); FDA (2015)</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Metabolism, metabolites 37% in the urine and 47% in the feces (4% as parent in each)</td>
<td>CYP3A4</td>
<td>P-gp</td>
<td>FDA (2015f)</td>
</tr>
<tr>
<td>Deoxycylcholic acid</td>
<td>Not metabolized, excreted in the feces as parent</td>
<td>None</td>
<td>BSEP</td>
<td>FDA (2015e)</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>Not metabolized, 82% in the feces and 0.12% in the urine (percentage of parent versus metabolites not assessed)</td>
<td>None</td>
<td>OAT3, OATP1B1, BSEP, MRP2</td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Metabolism in plasma, 58% in the urine and 35% in the feces</td>
<td>Nucleotidases</td>
<td>N/T</td>
<td>FDA (2015o)</td>
</tr>
<tr>
<td>Lumacaftor (and ivacaftor)</td>
<td>Not extensively metabolized, biliary excretion, 51% in the feces as parent</td>
<td>Mainly via oxidation and glucuronidation enzymes</td>
<td>N/T</td>
<td>FDA (2015r)</td>
</tr>
<tr>
<td>Sacubitril (and valsartan)</td>
<td>Metabolism, 51.7%–67.8% in the urine and 36.9%–48.3% in the feces (mainly as active metabolite LBQ657)</td>
<td>Esterases</td>
<td>P-gp, LBQ657: OATP1B1/5, OAT3</td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Metabolism, 46% in the feces (14% as parent) and 25% in the urine (parent &lt;1%)</td>
<td>CYP3A4, CYP2D6</td>
<td>P-gp, BCRP</td>
<td>FDA (2015t)</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>Metabolism, 70% in the feces and 30% in the urine</td>
<td>CYP3A4</td>
<td>None</td>
<td>FDA (2015u)</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Metabolism, biliary excretion, 88% in the feces (53% as parent), 6.6% in the urine (primarily as parent)</td>
<td>CYP3A, CYP2C8</td>
<td>P-gp</td>
<td>FDA (2015v)</td>
</tr>
<tr>
<td>Fibinanserin</td>
<td>Metabolism, 51% in the feces and 44% in the urine (primarily as parent)</td>
<td>CYP3A4, CYP2C19</td>
<td>None</td>
<td>FDA (2015w)</td>
</tr>
<tr>
<td>Rolapitant</td>
<td>Metabolism, biliary excretion, 73% in the feces (mainly as parent) and 14% in the urine (primarily as metabolites)</td>
<td>CYP3A4</td>
<td>None</td>
<td>FDA (2015x)</td>
</tr>
<tr>
<td>Uridine triacetate</td>
<td>Metabolism and catabolism, renal excretion</td>
<td>Esterases</td>
<td>P-gp, nucleoside transporters</td>
<td>FDA (2015y)</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Metabolism, 40.1% in the feces and 20.8% in the urine (parent and active metabolites accounts for 6%–8% overall in both)</td>
<td>CYP3A4, CYP2D6, glucuronidation and sulfation enzymes</td>
<td>None</td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td>Trifluridine (and tipiracil)</td>
<td>Not metabolized, mainly renal excretion as parent, no mass balance study</td>
<td>None</td>
<td>N/T</td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>Insulin delgudec</td>
<td>Proteolytic degradation</td>
<td>N/T, mostly by proteolytic enzymes</td>
<td>N/T</td>
<td>FDA (2015b)</td>
</tr>
<tr>
<td>Aripiprazole lauroxil</td>
<td>Hepatic metabolism</td>
<td>Parent: esterase- and water-mediated hydrolysis, aripiprazole: CYP3A4 and CYP2D6</td>
<td>N/T</td>
<td>FDA (2015c)</td>
</tr>
</tbody>
</table>

(continued)
of prodrugs) were also found to inhibit specific P450 enzymes (Table 3). With regard to the mechanism of inhibition, 10 NMEs and three metabolites were evaluated for time-dependent inhibition of P450 enzymes, and a majority, comprising eight NMEs and two metabolites, showed time-dependent inhibition of one or more P450 enzymes, in particular, CYP3A4/5. Alectinib and palbociclib, both the parent drugs and the metabolites (alectinib metabolite M4 and palbociclib metabolite M17) were time-dependent inhibitors of CYP3A4/5.

Based on the R1 and R2 values (FDA, 2012), the majority of the in vitro inhibitory interactions were not considered clinically relevant (R1 or R2 ≤ 1.1). Among drugs with R1 ≤ 1.1 and R2 > 1.1 (n = 11), in vivo studies and PBPK simulations with P450 probe substrates found only four NMEs with positive enzyme inhibition: isavuconazole (dosing regimen unavailable) and rolapitant (200 mg single dose) were found to moderately inhibit probe substrates of CYP3A (midazolam AUC ratio = 2.03, Cmax ratio = 1.72) and CYP2D6 (dextromethorphan AUC ratio = 3.33, Cmax ratio = 2.77), respectively; panobinostat (200 mg orally once daily) was a weak-to-moderate inhibitor of CYP2D6 (dextromethorphan AUC ratio = 1.20–2.30, Cmax ratio = 1.20–2.30); filibanserin (50 mg orally twice daily) was a weak inhibitor of CYP3A (simvastatin AUC ratio = 1.13, Cmax ratio = 1.15; simvastatin acid AUC ratio = 1.47, Cmax ratio = 1.36), and rolapitant (200 mg single dose) was a weak inhibitor of CYP2B6 (efavirenz AUC ratio = 1.32, Cmax ratio = 1.09) and CYP2C19 (omeprazole AUC ratio = 1.34, Cmax ratio = 1.48). The moderate (isavuconazole and rolapitant) and weak-to-moderate (panobinostat) inhibition interactions were all reflected in the respective labels (FDA, 2015i,1z). As expected, the majority of drugs with R values below the cut-off value of 1.1 were not evaluated clinically. However, those that were assessed in a clinical study actually showed weak inhibition of P450 enzymes: lesinurad (400 mg single dose; repaglinide AUC ratio = 1.31, Cmax ratio = 1.27) and rolapitant (200 mg single dose; repaglinide AUC ratio = 1.27, Cmax ratio = 1.26) showed weak inhibition of CYP2C8; and palbociclib (125 mg once daily) showed weak inhibition of CYP3A4 (midazolam AUC ratio = 1.58, Cmax ratio = 1.38). The effects of lesinurad and rolapitant were not considered clinically significant and no dose adjustment is needed, whereas the label for palbociclib specifies that “the dose of sensitive CYP3A substrates with a narrow therapeutic index (NTI) may need to be reduced as concurrent administration of palbociclib may increase their exposure” (FDA, 2015n). Of note, two drugs with R1 values > 1.1 (namely, sonidegib and osimertinib) had not been evaluated clinically at the time of their approval. Sonidegib was a potent inhibitor of CYP2B6 (Ki = 0.045 μM, R1 = 34) and CYP2C9 (Ki = 1.7 μM, R1 = 1.8) in vitro, and clinical studies to evaluate the effect of sonidegib on these two enzymes are currently being performed by the sponsor. For osimertinib, which showed in vitro inhibition of CYP3A (IC50 = 5.1 μM, R1 > 1.1), a clinical study to evaluate the effect of repeated dosing of osimertinib on the PK of a CYP3A probe substrate was requested as a postmarketing requirement (PMR). On the basis of the in vitro study results, concomitant administration of osimertinib with sensitive substrates of CYP3A4 should be avoided (FDA, 2015x).

When evaluating the in vitro findings by enzyme, the largest number of NMEs (15 drugs and seven metabolites, including two active metabolites from prodrugs) showed inhibition of CYP3A4/5 (Fig. 1B); however, only three NMEs showed positive inhibition of CYP3A4/5 clinically as discussed previously. A significant number of NMEs (eight drugs and two active metabolites including one from a prodrug) showed

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Main Elimination Route</th>
<th>Enzyme Involved</th>
<th>Transporter Involved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patiromer</td>
<td>Not absorbed or metabolized, entirely excreted in the feces</td>
<td>N/T (not likely to be metabolized)</td>
<td>N/T</td>
<td>FDA (2015b)</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Metabolism, 58% in the feces and 6% in the urine (negligible as parent if each)</td>
<td>CYP3A4, other P450s (not specified)</td>
<td>P-gp</td>
<td>FDA (2015f)</td>
</tr>
<tr>
<td>Elvitegravir, cobicistat, emtricitabine (and tenofovir alafenamide fumarate)</td>
<td>Metabolism, renal excretion (mainly as active metabolite tenofovir)</td>
<td>CYP3A, UGT2B7</td>
<td>P-gp, BCRP, OAT1B1/3</td>
<td>FDA (2015m)</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>Metabolism, 76% in the feces (6.6% as parent) and 18% in the urine (1.6% as parent)</td>
<td>CYP3A4, CYP2C8, CYP2C9, CYP2D6</td>
<td>P-gp</td>
<td>FDA (2015h)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Metabolism, 68% in the feces and 14% in urine (2% as parent overall in both)</td>
<td>CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9</td>
<td>P-gp, BCRP</td>
<td>FDA (2015x)</td>
</tr>
<tr>
<td>Ixazomib citrate</td>
<td>Metabolism, 62% in the urine (&lt;3.5% as parent) and 22% in the feces (mainly as active metabolite ixazomib)</td>
<td>CYP3A4, CYP2C8, CYP2C9, CYP2D6</td>
<td>P-gp</td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Metabolism, biliary excretion, 98% in the feces (84% as parent) and &lt;0.5% in the urine</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C9</td>
<td>N/T</td>
<td>FDA (2015b)</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>Mainly renal excretion, metabolism (&lt;3%)</td>
<td>N/T (not likely to be metabolized by P450s or the liver)</td>
<td>N/T</td>
<td>FDA (2015e)</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Metabolism, 93% in the feces and 12% in the urine</td>
<td>Carboxysterase 1, carboxysterase 2, CYP2C8, CYP3A4, UGT1A3, UGT2B7</td>
<td>P-gp, OAT1B1/3</td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td>Lesinurad</td>
<td>Metabolism, 63% in the urine and 32% in the urine (64% as metabolites in both and 31% was excreted in urine as parent)</td>
<td>CYP2C9, CYP1A1, CYP2C9, CYP3A, epoxide hydrolase</td>
<td>OAT1/3, OAT1B1/3, OCT1, BCRP</td>
<td>FDA (2015g)</td>
</tr>
</tbody>
</table>
TABLE 3
Enzyme inhibition interactions, in vitro to in vivo translation

PMR indicates the study was requested as a PMR. The inhibition studies were performed using human liver microsomes except cholic acid and ivabradine, for which the inhibition studies were performed using recombinant enzymes. If the in vitro substrate was not provided, then it is not listed; either CYP3A or CYP3A4 was used depending on how the enzyme was presented in the NDA reviews.

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>IC₅₀ (µM)</th>
<th>R₁ or R₂</th>
<th>AUC Ratio</th>
<th>Cₘ₅₀ Ratio</th>
<th>In Vivo Victim</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>2.0 (Kᵢ, competitive) (CYP2C8)</td>
<td>1.6⁵&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.06&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Repaglinide</td>
<td>FDA (2015b)</td>
</tr>
<tr>
<td></td>
<td>Kᵢ ≥ 60, Kₘ₅₀ = 0.0624/minute (CYP3A4)</td>
<td>N/A</td>
<td>0.97</td>
<td>0.92</td>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td>Alectinib</td>
<td>3.69, Kₘ₅₀ = 0.0620/minute (CYP3A4)</td>
<td>N/A</td>
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<tr>
<td>metabolite M4</td>
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<tr>
<td>Brexpiprazole</td>
<td>8.19 (CYP2D6, bupropion), 5.01 (Kᵢ, inhibition type N/P), no TDI observed</td>
<td>1.092</td>
<td>1.02</td>
<td>0.96</td>
<td>Bupropion</td>
<td>FDA (2015v)</td>
</tr>
<tr>
<td></td>
<td>22.23 (CYP2C9, diclofenac), no TDI observed</td>
<td>1.041</td>
<td>N/T</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>39.82 [CYP2C19, (S)-mephénytoïn], no TDI observed</td>
<td>1.023</td>
<td>N/T</td>
<td></td>
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<tr>
<td></td>
<td>13.44 (CYP2D6, bufuralol), no TDI observed</td>
<td>1.068&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.96</td>
<td></td>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.88, Kᵢ = 32.1, Kₘ₅₀ = 0.02/minute, Kₘ₅₀ = 0.00002/minute (CYP3A, midazolam)</td>
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<tr>
<td></td>
<td>40.78, Kᵢ = 4.7, Kₘ₅₀ = 0.022/minute, Kₘ₅₀ = 0.0016/minute (CYP3A, testosterone)</td>
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<td>Cangrelor</td>
<td>58–59 (CYP2C19)</td>
<td>&lt;1.1</td>
<td>N/T</td>
<td></td>
<td></td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>metabolite AR-C69712</td>
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<tr>
<td>Cangrelor</td>
<td>58–59 (CYP2C19)</td>
<td>&lt;1.1</td>
<td>N/T</td>
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<td></td>
<td>FDA (2015a)</td>
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<tr>
<td>metabolite AR-C90439</td>
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<tr>
<td>Cariprazine&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Weak (value N/P, CYP1A2)</td>
<td>N/A</td>
<td></td>
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<td>FDA (2015zd)</td>
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<tr>
<td>weak (value N/P, CYP2A6)</td>
<td>N/A</td>
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<tr>
<td>weak (value N/P, CYP2C9)</td>
<td>N/A</td>
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<tr>
<td>weak (value N/P, CYP2C19)</td>
<td>N/A</td>
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<tr>
<td>weak (value N/P, CYP2D6)</td>
<td>N/A</td>
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<tr>
<td>weak (value N/P, CYP2E1)</td>
<td>N/A</td>
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<tr>
<td>weak (value N/P, CYP3A4)</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Cariprazine metabolites DCAR</td>
<td>Weak (value N/P, CYP1A2)</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>weak (value N/P, CYP2C9)</td>
<td>N/A</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>weak (value N/P, CYP2D6)</td>
<td>N/A</td>
<td></td>
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<tr>
<td>weak (value N/P, CYP3A4)</td>
<td>N/A</td>
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<tr>
<td>Cariprazine metabolites DDCAR</td>
<td>Weak (value N/P, CYP1A2)</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td>FDA (2015a)</td>
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<tr>
<td>weak (value N/P, CYP2C9)</td>
<td>N/A</td>
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<tr>
<td>weak (value N/P, CYP2D6)</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td>weak (value N/P, CYP3A4)</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Cholic acid</td>
<td>38.1% (P &lt; 0.01) at 100 µM (UGT1A1, 4-methylumbelliferone)</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td>Fang et al. (2013); FDA (2015f)</td>
</tr>
<tr>
<td></td>
<td>13.9% (P &lt; 0.05) at 100 µM (UGT1A8, 4-methylumbelliferone)</td>
<td>N/A</td>
<td></td>
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<tr>
<td></td>
<td>25.65% (P &lt; 0.01) at 100 µM (UGT1A10, 4-methylumbelliferone)</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>27.9% (P &lt; 0.01) at 100 µM (UGT2B15, 4-methylumbelliferone)</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>1.8 (unbound Kᵢ) (CYP2D6, bufuralol)</td>
<td>1.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.65</td>
<td>0.92</td>
<td>Dextromethorphan</td>
<td>FDA (2015h)</td>
</tr>
<tr>
<td></td>
<td>5.9 (CYP3A, testosterone); 17.76 (unbound Kᵢ) (CYP3A, midazolam)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Daclatasvir</td>
<td>11.0 (CYP3A4, testosterone), 31.8 (CYP3A4, midazolam), no TDI observed</td>
<td>1.2²&lt;sup&gt;e&lt;/sup&gt; (testosterone), 1.1¹&lt;sup&gt;e&lt;/sup&gt; (midazolam)</td>
<td>1.02</td>
<td>1.05</td>
<td>Midazolam</td>
<td>FDA (2015j)</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>20 (CYP2E1, chloroxazone) ~5% (coincubation) and 42% (preincubation) at 50 µM (CYP3A4, midazolam)</td>
<td>1.00&lt;sup&gt;f&lt;/sup&gt;</td>
<td>N/T</td>
<td>0.94</td>
<td>Ethinyl estradiol</td>
<td>FDA (2015zc)</td>
</tr>
<tr>
<td></td>
<td>1% (coincubation) and 30%–40% (preincubation) at 50 µM (CYP3A4, testosterone)</td>
<td>N/A</td>
<td>1.05</td>
<td>0.98</td>
<td>Norethindrone</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
TABLE 3—Continued

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>IC₅₀</th>
<th>R₁ or R₂</th>
<th>AUC Ratio</th>
<th>Cₘₐₓ Ratio</th>
<th>In Vivo Victim</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin</td>
<td>6.4 (Kᵢ) (CYP2B6)</td>
<td>1.17*ₙₑ</td>
<td>1.03</td>
<td>1.03</td>
<td>Bupropion Simvastatin</td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td></td>
<td>7.5 (Kᵢ) (CYP3A4)</td>
<td>1.14*ₙₑ</td>
<td>1.31, simvastatin acid 1.47</td>
<td>1.5, simvastatin acid 1.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isavuconazonium sulfate metabolite isavuconazole</td>
<td>2.86 (Kᵢ) (CYP2C8)</td>
<td>6.98*ₙₑ</td>
<td>No effect (value N/P)</td>
<td>No effect (value N/P)</td>
<td>Repaglinide</td>
<td>FDA (2015i)</td>
</tr>
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<tr>
<td></td>
<td>4.78 (Kᵢ) (CYP2C9)</td>
<td>4.58*ₙₑ</td>
<td>No effect (value N/P)</td>
<td>No effect (value N/P)</td>
<td>(S)-warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.40 (Kᵢ) (CYP2C19)</td>
<td>4.17*ₙₑ</td>
<td>No effect (value N/P)</td>
<td>No effect (value N/P)</td>
<td>Omeprazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.82 (Kᵢ) (CYP2D6)</td>
<td>4.55*ₙₑ</td>
<td>No effect (value N/P)</td>
<td>No effect (value N/P)</td>
<td>Dextromethorphan</td>
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<tr>
<td></td>
<td>6.22–1.93 (Kᵢ) (CYP3A4)</td>
<td>9.86–28.49*ₙₑ</td>
<td>2.03</td>
<td>1.72</td>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>46 (CYP3A4, midazolam)</td>
<td>1.00</td>
<td>N/T</td>
<td></td>
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<td>FDA (2015g)</td>
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<tr>
<td></td>
<td>17 (CYP3A5, midazolam)</td>
<td>1.01*ₙₑ</td>
<td>N/T</td>
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<td>140 (Kᵢ) (CYP3A4, midazolam)</td>
<td>1.00*ₙₑ</td>
<td>N/T</td>
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<tr>
<td></td>
<td>Lenvatinib</td>
<td>1.20–1.31*ₙₑ</td>
<td>1.01*ₙₑ</td>
<td>1.21*ₙₑ</td>
<td>Midazolam</td>
<td>FDA (2015q)</td>
</tr>
<tr>
<td></td>
<td>10.1 (CYP2C8, paclitaxel)</td>
<td>1.95*ₙₑ</td>
<td>N/P</td>
<td></td>
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<tr>
<td></td>
<td>10.6 (UGT1A1, estradiol)</td>
<td>1.19–1.29*ₙₑ</td>
<td>N/T</td>
<td></td>
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<tr>
<td></td>
<td>14.0 (UGT1A4, trifluoperazine)</td>
<td>1.14–1.22*ₙₑ</td>
<td>N/T</td>
<td></td>
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<tr>
<td></td>
<td>Lesinurad</td>
<td>1.20–1.29*ₙₑ</td>
<td>1.27</td>
<td>1.06</td>
<td></td>
<td>FDA (2015zg)</td>
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<td></td>
<td>16.2 (CYP2C8)</td>
<td>1.00*ₙₑ</td>
<td>1.31</td>
<td></td>
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<tr>
<td></td>
<td>40.7 (CYP2C9)</td>
<td>1.00*ₙₑ</td>
<td>1.04</td>
<td></td>
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<tr>
<td></td>
<td>148 (UGT1A1)</td>
<td>1.00*ₙₑ</td>
<td>1.11</td>
<td></td>
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<tr>
<td></td>
<td>384 (UGT2B7)</td>
<td>1.00*ₙₑ</td>
<td>N/T</td>
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<td></td>
<td>Lumacaftor</td>
<td>Value N/P (CYP2C8)</td>
<td>N/A</td>
<td></td>
<td></td>
<td>FDA (2015u)</td>
</tr>
<tr>
<td></td>
<td>Value N/P (CYP2C9)</td>
<td>N/A</td>
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<tr>
<td></td>
<td>Osimertinib</td>
<td>22.8 (CYP2C8)</td>
<td>&lt;1.1</td>
<td></td>
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<td>FDA (2015x)</td>
</tr>
<tr>
<td></td>
<td>5.1 (CYP3A)</td>
<td>&lt;1.1</td>
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<tr>
<td></td>
<td>Palbociclib</td>
<td>Kᵢ = 10, Kₘₐₓ = 0.036/minute (CYP3A, midazolam)</td>
<td>R₂ = 1.05 with kdeg = 1.18/minute</td>
<td>1.58</td>
<td>1.38</td>
<td>Midazolam</td>
</tr>
<tr>
<td></td>
<td>Kᵢ = 9, Kₘₐₓ = 0.087/minute (CYP3A, testosterone)</td>
<td>R₂ = 1.06 with kdeg = 0.18/minute</td>
<td>1.01 N/T</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Palbociclib metabolite M17</td>
<td>Kᵢ = 7.0, Kₘₐₓ = 0.094/minute (CYP3A, midazolam)</td>
<td>1.01</td>
<td>N/T</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Kᵢ = 6.4, Kₘₐₓ = 0.15/minute (CYP3A, testosterone)</td>
<td>1.03</td>
<td>N/T</td>
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<td></td>
<td>Panobinostat</td>
<td>15–75 (CYP2C19), no TDI observed</td>
<td>&lt;1.1</td>
<td>N/T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0.167 (Kᵢ) (CYP2D6), no TDI observed</td>
<td>1.37*ₙₑ</td>
<td>1.20–3.00</td>
<td>1.20–3.00</td>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15–75, Kᵢ = 12, Kₘₐₓ = 0.137/minute (CYP3A, testosterone)</td>
<td>1.04*ₙₑ</td>
<td>1.04*ₙₑ</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Panobinostat metabolite M17</td>
<td>16 (CYP3A, felodipine)</td>
<td>&lt;1.1</td>
<td>N/T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rolapitant</td>
<td>39% at 100 μM (coincubation), 90 (preincubation) (CYP1A2, phenacetin)</td>
<td>N/A</td>
<td>N/T</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>22 (coincubation), 10 (preincubation) (CYP2A6, coumarin)</td>
<td>N/A</td>
<td>N/T</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>13 (CYP2B6, bupropion), no TDI observed</td>
<td>1.13*ₙₑ</td>
<td>1.32</td>
<td>1.09</td>
<td>Efavirenz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 (CYP2C8, amodiaquine), no TDI observed</td>
<td>&lt;1.1</td>
<td>1.27</td>
<td>1.26</td>
<td>Repaglinide</td>
<td></td>
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<tr>
<td></td>
<td>9.6 (CYP2C9, diclofenac), no TDI observed</td>
<td>1.18*ₙₑ</td>
<td>1.05</td>
<td>0.96</td>
<td>Tolbutamide</td>
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<tr>
<td></td>
<td>8.7 (CYP2C19, (S)-mephentoyin), no TDI observed</td>
<td>1.20*ₙₑ</td>
<td>1.34</td>
<td>1.48</td>
<td>Omeprazole</td>
<td></td>
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<tr>
<td></td>
<td>7.1, 3.4 (Kᵢ, competitive) (CYP2D6, dextromethorphan), no TDI observed</td>
<td>1.50*ₙₑ</td>
<td>3.33</td>
<td>2.77</td>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>49 (coincubation), 35 (preincubation) (CYP3A4/5, testosterone)</td>
<td>&lt;1.1</td>
<td>0.97</td>
<td>0.87</td>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41 (coincubation), 28 (preincubation) (CYP3A4/5, midazolam)</td>
<td>&lt;1.1</td>
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</tbody>
</table>

(continued)
some inhibition of CYP2C8 in vitro (Fig. 1B). Three drugs (alectinib, lenvatinib, and isavuconazole) had R1 values > 1.1; however, when evaluated clinically or using PBPK modeling, none of them were expected to be significant clinical inhibitors of CYP2C8. In contrast, two drugs with R1 < 1.1 (namely, lesinurad and rolapitant) significantly increased the exposure of coadministered repaglinide, a CYP2C8 probe substrate, by approximately 30%. The remaining drugs with R1 values less than the cut-off value were not evaluated clinically; however, based on the in vitro study results, comitant use of the combination drug lumacaftor (also an in vitro inducer of CYP2C8) and ivacaftor with CYP2C8 substrates may alter the exposure of these substrates (FDA, 2015u,za).

Similarly, for CYP2C19, among all of the NMEs with positive in vitro inhibition results (six drugs and five metabolites, including two from prodrugs; see Fig. 1B), only rolapitant was found to weakly inhibit CYP2C19 in vivo, although the interaction was not considered clinically meaningful. Finally, with regard to CYP2D6, three NMEs and one active metabolite from a prodrug had R1 values > 1.1 and were evaluated clinically (Table 3), two of which (panobinostat and rolapitant) were found to be weak-to-moderate inhibitors of CYP2D6. On the basis of these study results, concurrent use of rolapitant with CYP2D6 substrates with a NTI is contraindicated (e.g., thioridazine) or should be avoided (e.g., pimozone). Similarly, concomitant use of panobinostat with sensitive CYP2D6 substrates or CYP2D6 substrates with a NTI should be avoided. In both cases, if concomitant use of CYP2D6 substrates is unavoidable, it is recommended to monitor patients for adverse reactions (FDA, 2015u,za).

In terms of enzyme induction potential, 27 (82%) NMEs were assessed using human hepatocytes, and 12 drugs were found to induce DME expression or activity, or activate pregnane X receptor (PXR) to some extent (Table 4): alectinib (CYP2B6 and CYP3A4), cangrelor (CYP2C9 and CYP3A4/5), cobimetinib (CYP3A4), daclatasvir (CYP2B6 and CYP3A4), deoxyxocholic acid (CYP1A2), lenvatinib (CYP3A4), lesinurad (CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5), lumacaftor (CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5), osimertinib (CYP1A2, CYP3A4/5, and PXR), rolapitant (CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5), selexipag (CYP3A4), and tenofivir alafenamide fumarate (PXR). Isavuconazole also showed some induction of CYP1A2, CYP2B6, CYP2C8, and
TABLE 4
Enzyme induction interactions, in vitro to in vivo translation

The R₃ values were not provided for any of the compounds listed. Induction experiments were conducted using human hepatocytes; either CYP3A or CYP3A4 was used depending on how the enzyme was presented in the NDA reviews.

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>Induction Effect</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>AUC Ratio</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Ratio</th>
<th>In Vivo Victim</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>µM</td>
<td></td>
<td></td>
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<tr>
<td>Alectinib</td>
<td>2.1-fold in mRNA at 1 µM (CYP2B6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FDA (2015b)</td>
</tr>
<tr>
<td></td>
<td>2.1-fold in mRNA at 1 µM (CYP3A4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.38</td>
<td>0.97</td>
<td>0.92</td>
<td>Midazolam</td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Induction observed at 100 µM, value N/P (significantly lower than positive control) (CYP2C9)</td>
<td>0.77</td>
<td>N/T</td>
<td></td>
<td></td>
<td>FDA (2015c)</td>
</tr>
<tr>
<td>Cangrelor metabolite</td>
<td>AR-C69712</td>
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</tr>
<tr>
<td></td>
<td>Induction observed at 100 µM, value N/P (significantly lower than positive control) (CYP2C9)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Induction observed at 100 µM, value N/P (significantly lower than positive control) (CYP3A4)</td>
<td></td>
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<tr>
<td>Cholic acid</td>
<td>0.4-fold (P &lt; 0.001) in mRNA at 50 µM (CYP3A4)</td>
<td>1.88</td>
<td>N/T</td>
<td></td>
<td></td>
<td>FDA (2015f); Zhang et al. (2015)</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>9.1-fold at 10 µM in mRNA (but not activity, also no PXR activation up to 25 µM) at 10 µM (CYP3A4&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>0.51</td>
<td>1.02</td>
<td>1.06</td>
<td>Midazolam</td>
<td>FDA (2015h)</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>0.458- to 1.36-fold with 0.5-fold observed in two lots at 9.6 µg/ml (CYP1A2)</td>
<td>2.34</td>
<td>N/T</td>
<td></td>
<td></td>
<td>FDA (2015j)</td>
</tr>
<tr>
<td></td>
<td>1.66- to 3.95-fold in mRNA at 9.6 µg/ml (CYP2B6)</td>
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<tr>
<td></td>
<td>8.76- to 27.3-fold in mRNA at 9.6 µg/ml (CYP3A4&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>0.85</td>
<td>0.94</td>
<td></td>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43% of positive control in activity at 10 µM in one out three lots (CYP1A2)</td>
<td>2.61</td>
<td>N/T</td>
<td></td>
<td></td>
<td>FDA (2015p)</td>
</tr>
<tr>
<td>Deoxycholic acid</td>
<td></td>
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<tr>
<td>Isavuconazonium sulfate</td>
<td>metabolite isavuconazole</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2.77-fold (≤10% of positive control) in activity (concentrations N/P) (CYP1A2)</td>
<td>17.14</td>
<td>No effect (value N/P)</td>
<td>No effect (value N/P)</td>
<td>Caffeine</td>
<td>FDA (2015g)</td>
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<tr>
<td></td>
<td>13.4-fold (84.3% of positive control) in activity (concentrations N/P) (CYP2B6)</td>
<td>0.58</td>
<td>0.69</td>
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<tr>
<td></td>
<td>2.63-fold (37.4% of positive control) in activity (concentrations N/P) (CYP2C9)</td>
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<tr>
<td></td>
<td>3.43-fold (42.2% of positive control) in activity (concentrations N/P) (CYP3A4&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>0.69</td>
<td>N/P</td>
<td></td>
<td>Ritonavine</td>
<td></td>
</tr>
<tr>
<td>Lumacaftor</td>
<td>Induction observed, value N/P (CYP2B6)</td>
<td>55.26</td>
<td>N/T</td>
<td></td>
<td></td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td></td>
<td>Induction observed, value N/P (CYP2C9)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Induction observed, value N/P (CYP3A4)</td>
<td></td>
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</table>

(continued)
CYP3A4/5. However, for most of the drugs these interactions were considered unlikely to have any clinical relevance, and in vivo only three NMEs showed clinical induction of P450 enzymes: lumacaftor (dosing regimen unavailable) was found to strongly induce CYP3A, causing an 80% decrease in the AUC of the coadministered ivacaftor, a sensitive substrate of CYP3A; isavuconazole (200 mg orally once daily administered as the prodrug isavuconazonium sulfate) was a weak inducer of both CYP2B6 (bupropion AUC ratio = 0.58, Cmax ratio = 0.69) and CYP3A (ritonavir AUC ratio = 0.69, Cmax ratio unavailable; lopinavir AUC ratio = 0.73, Cmax ratio unavailable); and lesinurad (400 mg orally once daily) weakly induced CYP3A (amlodipine AUC ratio = 0.58, Cmax ratio = 0.61). On the basis of these results, it is not recommended to administer lumacaftor/ivacaftor (as the combination drug ORKAMBI) with sensitive CYP3A substrates or CYP3A substrates with a NTI because of the risk of induction (FDA, 2015a). Similarly, it is suggested to consider a dose increase of bupropion and use lopinavir/ritonavir with caution when coadministered with isavuconazonium sulfate, and to monitor patients for a potential reduction in efficacy of sensitive CYP3A substrates with coadministration of lesinurad (FDA, 2015i,zg). Interestingly, almost all of the in vitro inducers also showed inhibition of the same P450 enzyme (Table 3). For example, rolapitant was found to increase CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 activities up to 3.0-fold at 10 μM in human hepatocytes and to also inhibit these enzymes in human liver microsomes with IC50 values of 23, 9.6, 8.7, and 41 μM, respectively; it was also a possible time-dependent inhibitor of CYP3A4/5. In vivo, overall inhibition of CYP2C8 and CYP2C19 was observed with a 30%—50% increase in the exposure to the respective substrates repaglinide and omeprazole, whereas rolapitant coadministration had no significant effects on the PK of CYP2C9 and CYP3A probe substrates tolbutamide and midazolam. Similarly, daclatasvir induced CYP3A4 mRNA expression by 27.3-fold and also inhibited CYP3A4/5 (IC50 = 11.0 and 31.8 μM for substrates testosterone and midazolam, respectively). However, when tested in vivo with the probe substrate midazolam, daclatasvir had no significant effect on CYP3A. Another interesting example is isavuconazole, which was shown to induce CYP2C8 and CYP3A4/5 activities in vitro, and to inhibit these two enzymes as well. In vivo, coadministration of the prodrug isavuconazonium sulfate (dosing regimen unavailable) did not affect the PK of the coadministered CYP2C8 probe substrate repaglinide; however, significant increases in the exposure of known substrates of CYP3A were observed, including tacrolimus (AUC ratio = 2.25, Cmax ratio = 1.42), midazolam (AUC ratio = 2.03, Cmax ratio = 1.72), sirolimus (AUC ratio = 1.84, Cmax ratio = 1.65), atorvastatin (AUC ratio = 1.40, Cmax ratio unavailable), and cyclosporine (AUC ratio = 1.30, Cmax ratio unavailable), whereas significant decreases in the exposure of ritonavir (AUC ratio = 0.69, Cmax ratio unavailable) and lopinavir (AUC ratio = 0.79, Cmax ratio unavailable) were observed after metabolism by CYP3A, were observed. Finally, no effect was observed on oral contraceptives or prednisone, suggesting that the net effect (inhibition or induction) of isavuconazole on CYP3A was substrate dependent. Similar to the NDA approvals in previous years (Yu et al., 2014, 2016), nuclear receptors were not commonly investigated. Indeed, only five NMEs (cobimetinib, ivabradine, osimertinib, sonidegib, and tenofovir alafenamide fumarate) were evaluated for PXR activation and one (tenofovir alafenamide fumarate) for aryl hydrocarbon receptor activation together with P450 induction assessment (except ivabradine, which was only evaluated for PXR activation). As a result, osimertinib and tenofovir alafenamide fumarate showed PXR activation. However, in contrast to osimertinib, which was also found to induce CYP3A activity, no induction of CYP3A mRNA expression (activity not measured) was observed in human hepatocytes with tenofovir alafenamide fumarate at concentrations up to 100 μM.
Interestingly, among the three drugs without PXR activation, cobimetinib was found to induce CYP3A4 mRNA expression by 9.1-fold at 10 μM, indicating induction of CYP3A4 independent of PXR regulation. In addition to P450, lenvatinib, panobinostat, and tenofovir alafenamide fumarate were investigated for their induction potential of UGT (including UGT1A1/4A and UGT2B7). Induction of transporters was also evaluated in two cases: panobinostat for the induction of P-gp and multidrug resistance-associated protein (MRP) 2 (MRP2), and tenofovir alafenamide fumarate for P-gp. However, no induction was observed in these preclinical studies.

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

Transport and Transporter-Mediated DDIs

Out of the 33 NDA approval packages released by the FDA in 2015, 25 (76%) contained in vitro transport data involving a total of 37 compounds (25 parent drugs plus 12 metabolites, including three metabolites of prodrugs). In the past 3 years, there has been a consistent increase in the number of NDA approval packages, which include in vitro transport data, reflective of the increased emphasis on in vitro transporter assays by the regulatory agencies (European Medicines Agency, 2012; FDA, 2012; Pharmaceuticals and Medical Devices Agency, 2014). Notably, in 2016, for one NDA (lesinurad), a treatment of hyperuricemia associated with gout, inhibition of a urate transporter (urate anion exchanger 1) is the mechanism of action (clinical trials of which are not included in the subsequent statistics). To follow up on the in vitro studies, seven NMEs were tested as in vivo substrates of P-gp, BCRP, organic anion-transporting polypeptides (OATPs) OATP1B1/3, organic cation transporter (OCT) 2 (OCT2), organic anion transporter (OAT) 3 (OAT3), or MRP2. More than 20 clinical trials were performed using the NME as the victims with clinical inhibitors or inducers, resulting in nine positive studies (AUC ratio ≥ 1.25 or ≤ 0.8). Similarly, more than 20 clinical studies were performed to investigate 10 NMEs as in vivo inhibitors of P-gp, BCRP, OATP1B1/3, OAT1/3, and OCT1 using the NME as the perpetrator, with 10 showing positive results.

Overall, the number of transporters tested in in vitro assays increased with respect to previous years (16 in 2013 and 19 in 2014), with 21 individual transporters tested: P-gp, BCRP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT2, OAT3, OAT4, OCT1, OCT2, OCT3, multidrug and toxin extrusion proteins MATE1 and MATE2-K, bile salt export pump, MRP2, MRP4, urate anion exchanger 1, sodium-taurocholate cotransporting polypeptide, apical sodium-dependent bile acid transporter, and sodium-phosphate transporter NPT1. Similar to 2014, almost 400 transporter assays were described within the approval packages, with a majority of the assays performed using the NME as an inhibitor. More than one-third of the in vitro substrate assays were positive, while one-half of the in vitro inhibition assays were positive.

As was the case in 2013 and 2014, P-gp was the most tested transporter in vitro in terms of substrates (30 out of 37 NMEs, including parent drugs and metabolites), and had the most positive interactions—19 NMEs, comprising 16 parent drugs and four metabolites (Fig. 2A). Of the 16 parent drugs identified as in vitro substrates (alectinib, cobimetinib, daclatasvir, edoxaban, eluxadoline, ixazomib, ivabradine, lenvatinib, osimertinib, palbociclib, panobinostat, sacubitril, selexipag, tenofovir alafenamide fumarate, trabectedin, and uridine triacetate), six were tested as in vivo substrates; with all six showing positive interactions, four of which had victim AUC ratios ≥ 2. The largest interaction identified was when ivabradine was coadministered with ketoconazole (200 mg orally once daily; ivabradine AUC ratio = 7.70, Cmax ratio = 3.60), although this effect was likely due to CYP3A inhibition as well, as discussed in the metabolism section, ivabradine being also a substrate of CYP3A and ketoconazole being a strong CYP3A inhibitor. Likewise, the interaction between daclatasvir and simprevir (150 mg orally once daily; daclatasvir AUC ratio = 2.20, Cmax ratio = 1.60) could also be, at least partially, mediated by CYP3A (simprevir has been shown to weakly inhibit intestinal CYP3A) (FDA, 2015g). Interestingly, cyclosporine, also a P-gp inhibitor, had no clinically relevant effect on daclatasvir PK. The next largest interactions were when prodigro tenofovir alafenamide fumarate was coadministered with cobicistat (150 mg orally once daily; tenofovir alafenamide fumarate AUC ratio = 2.65, Cmax ratio = 2.80; active metabolite tenofovir AUCmax ratio = 3.31, Cmax ratio = 3.34) and selexipag was coadministered with lopinavir/ritonavir (dosing regimen unavailable; selexipag AUC ratio = 2.00, Cmax ratio = 2.00), although these interactions could be due to inhibition of other transporters in addition to P-gp (BCRP and OATP1B1/3, and OATP1B1/3, respectively). Edoxaban was evaluated with seven different P-gp inhibitors, including amiodarone (400 mg orally once daily), cyclosporine (500 mg orally single dose), dromedarone (400 mg orally twice daily), erythromycin (500 mg orally four times daily), ketoconazole (400 mg orally once daily), quinidine (300 mg orally three times daily) and verapamil (240 mg orally once daily), all of which increased edoxaban AUC and Cmax by 40%–90%. Lenvatinib was evaluated in vivo with both ketoconazole and rifampin as the inhibitors; while ketoconazole had no effect, rifampin (600 mg orally single dose) had a small effect on lenvatinib exposure (AUC ratio = 1.30, Cmax ratio = 1.32). Regarding in vivo induction of P-gp, two NMEs were evaluated, edoxaban and lenvatinib, using multiple doses of rifampin. For edoxaban, the AUC
ratio was 0.60, with no effect of rifampin on $C_{\text{max}}$; whereas for lenvatinib, the AUC ratio was 0.83 and the $C_{\text{max}}$ ratio was 0.98, and there was a 23% increase in lenvatinib clearance.

Roughly an equal number of NMEs were evaluated in vitro as substrates of OATP1B1, OATP1B3, and BCRP (16, 15, and 16, respectively), and approximately two-thirds were evaluated against OAT1/3, OCT1/2, and MRP2, with less than one-half of these interactions showing a positive result. As mentioned previously, in addition to P-gp, the interaction of tenofovir alafenamide fumarate with the remaining six drugs, the coadministration of NMEs with OAT1B1 inhibitors as well as to monitor for adverse events (FDA, 2015zc). A smaller interaction was observed when lenvatinib, for which the clinical effect was not investigated. As a result, daclatasvir (60 mg orally once daily) and eluxadoline (100 mg single dose) were found to increase the AUC and $C_{\text{max}}$ values of coadministered rosuvastatin by 40%–47% and 18%–84%, respectively; isavuconazonium sulfate and sacubitril (dosing regimen unavailable for both) increased the atorvastatin AUC value by 30%–40% and $C_{\text{max}}$ value by 5%–75%, whereas the coadministration of lesinurad had no effect on atorvastatin PK (atorvastatin AUC ratio = 1.01, $C_{\text{max}}$ ratio = 1.17).

Eleven NMEs and three metabolites were shown to be in vitro inhibitors of BCRP, with three NMEs (cariprazine, lesinurad, and selexipag) not triggering clinical trials based on in vitro data ([I]$_2$/[IC50] < 0.1 and/or [I]$_2$/IC50 < 10, where [I]$_2$ is the total $C_{\text{max}}$ value representing systemic exposure and [I]$_1$ is the highest dose in mol/250 ml to represent intestinal exposure). For seven of the remaining eight parent compounds, both the [I]$_2$/IC50 and [I]$_2$/IC50 values were greater than the FDA cut-off values, and for osimertinib only the [I]$_1$/IC50 value was greater (Table 6). Clinical studies were undertaken for brexpiprazole, daclatasvir, isavuconazonium sulfate, and rolapitant. No effect was observed with brexpiprazole (rosuvastatin as the victim drug) or isavuconazonium.

### TABLE 5

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>OATP</th>
<th>In Vitro Substrate</th>
<th>IC50</th>
<th>$C_{\text{max}}$/IC50</th>
<th>AUC Ratio</th>
<th>$C_{\text{max}}$ Ratio</th>
<th>In Vivo Victim</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brexpiprazole</td>
<td>I1B</td>
<td>Estradiol 17-β-glucuronide</td>
<td>8.39</td>
<td>0.05</td>
<td>N/T</td>
<td>N/T</td>
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<td>FDA (2015v)</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>I1B</td>
<td>Estradiol 17-β-glucuronide</td>
<td>9.13</td>
<td>0.01</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015h)</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>I1B</td>
<td>Estrone-3-sulfate</td>
<td>118</td>
<td>0.1</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015f)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>Fluo-3</td>
<td>85</td>
<td>0.1</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015m)</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>I1B</td>
<td>BMS-791553</td>
<td>2.3</td>
<td>1.02$^{a,b}$</td>
<td>1.47</td>
<td>1.84</td>
<td>Rosuvastatin</td>
<td>FDA (2015j)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>Cholecytokinin octapeptide</td>
<td>5.7</td>
<td>0.41$^{a,b}$</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Deoxycyclic acid</td>
<td>I1B</td>
<td>N/P</td>
<td>N/P</td>
<td>0.14$^b$</td>
<td>N/T, $R &lt; 1.25$</td>
<td>N/T</td>
<td></td>
<td>FDA (2015p)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>N/P</td>
<td>N/P</td>
<td>0.11$^b$</td>
<td>N/T, $R &lt; 1.25$</td>
<td>N/T</td>
<td></td>
<td>FDA (2015w)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>I1B</td>
<td>N/P</td>
<td>62.7</td>
<td>0.01$^a$</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015x)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>N/P</td>
<td>50.8</td>
<td>0.01$^a$</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>I1B</td>
<td>Estradiol 17-β-glucuronide</td>
<td>32.6%</td>
<td>0.05</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td></td>
<td>I1B</td>
<td>N/P</td>
<td>11.2</td>
<td>1.53$^{a,b}$</td>
<td>1.40</td>
<td>1.05</td>
<td>Rosuvastatin</td>
<td>FDA (2015f)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>N/P</td>
<td>9.3</td>
<td>1.89</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>I1B</td>
<td>Estradiol 17-β-glucuronide</td>
<td>11.2</td>
<td>1.53$^{a,b}$</td>
<td>1.40</td>
<td>1.05</td>
<td>Atorvastatin</td>
<td>FDA (2015i)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>N/P</td>
<td>43.1</td>
<td>0.85</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>I1B</td>
<td>N/P</td>
<td>22</td>
<td>0.05</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>N/P</td>
<td>52.5</td>
<td>0.02</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015x)</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>I1B</td>
<td>N/P</td>
<td>N/P</td>
<td>3.11$^b$</td>
<td>1.30</td>
<td>1.75</td>
<td>Atorvastatin</td>
<td>FDA (2015i)</td>
</tr>
<tr>
<td>Sacubitril</td>
<td>I1B</td>
<td>N/P</td>
<td>1.9</td>
<td>1.55$^{a,b}$</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015x)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>N/P</td>
<td>3.8</td>
<td>1.55$^{a,b}$</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015k)</td>
</tr>
<tr>
<td>Sacubitril metabolite</td>
<td>I1B</td>
<td>LBQ657</td>
<td>126</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td>Selexipag</td>
<td>I1B</td>
<td>Atorvastatin</td>
<td>2.4</td>
<td>0.03$^a$</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>Taurocholic acid</td>
<td>1.7</td>
<td>0.02$^a$</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td>Selexipag metabolite</td>
<td>I1B</td>
<td>Atorvastatin</td>
<td>3.5</td>
<td>N/A</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>Taurocholic acid</td>
<td>4.1</td>
<td>N/A</td>
<td>N/T</td>
<td>N/T</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td>Tenofovir alafenamide</td>
<td>I1B</td>
<td>Fluo-3</td>
<td>29.8%</td>
<td>0.01</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td></td>
<td>I3B</td>
<td>Fluo-3</td>
<td>25.5%</td>
<td>0.01</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>FDA (2015z)</td>
</tr>
</tbody>
</table>

N/A, not applicable; N/P, not provided; N/T, not tested.

$^a$Ratio was calculated by the University of Washington Drug Interaction Database editorial team.

$^b$Values exceed the FDA cut-off value of 0.1.
sulfate (methotrexate as the victim drug). Both daclatasvir and rolapitant caused changes in the victim PK, with the larger effect by rolapitant (200 mg single dose) when coadministered with sulfasalazine (sulfasalazine AUC ratio = 2.18, C\text{max} ratio = 2.38). Therefore, increased plasma concentration of BCRP substrates with a NTI may result in potential adverse reactions with concurrent use of rolapitant, and patients should be monitored for adverse reactions related to the concomitant drug (FDA, 2015za). The effect of daclatasvir (60 mg orally once daily) on rosuvastatin exposure was also considered clinically significant (rosuvastatin AUC ratio = 1.47, C\text{max} ratio = 1.84). As mentioned previously, note that inhibition of OATP1B1/3 may also be involved in the interaction of daclatasvir and rosuvastatin. For the remaining four NMEs, the in vitro data suggested possible in vivo inhibition of BCRP; however, no clinical studies were undertaken. A clinical study was requested for osimertinib as a PMR to evaluate the effect of repeated doses of osimertinib on the PK of a probe substrate of BCRP. Similarly, it was recommended to conduct such studies for alectinib in comments from the FDA reviewers. It is worth noting that while four clinical trials were undertaken to study inhibition of BCRP, three different victim drugs were used (methotrexate, rosuvastatin, and sulfasalazine), highlighting the need for the identification of an appropriate BCRP probe substrate (Lee et al., 2015).

Concerning inhibition of P-gp, a total of 14 NMEs were shown to be in vitro inhibitors, comprising nine parent drugs and five metabolites. For two NMEs (cariprazine and lenisurad) no clinical studies were triggered based on the in vitro inhibition data (Table 7). Interestingly, four NMEs (brexpiprazole, edoxaban, ivabradine, and sacubitril) either did not inhibit P-gp in vitro or inhibition was deemed not clinically relevant ([I]/IC\text{50} < 0.1) or [I]/IC\text{50} < 10); however, the sponsor still performed in vivo clinical studies with a P-gp probe substrate. Indeed, brexpiprazole had no effect on fexofenadine PK, and edoxaban and sacubitril had no effect on digoxin PK. In the case of ivabradine, while the parent compound did not inhibit P-gp in vitro, the metabolite S18982 showed minor inhibition of P-gp, with an IC\text{50} of 5.3 \mu M. However, this is at least two orders of magnitude greater than the total plasma concentration; therefore, it is unlikely to cause systemic inhibition, which was confirmed in an in vivo clinical trial, where ivabradine had no effect on digoxin PK. In vitro data for the remaining six NMEs (daclatasvir, flibanserin, isavuconazonium sulfate, rolapitant, alectinib, and uridine triacetate) showed that at least one of the [I]/IC\text{50} values was greater than the FDA cut-off value. When evaluated clinically with the P-gp probe substrate digoxin, daclatasvir (60 mg orally once daily), flibanserin (100 mg orally once daily), isavuconazonium sulfate (200 mg orally once daily), and rolapitant (180 mg orally single dose) all showed significant increases in the exposure to digoxin, with AUC ratios of 1.27, 1.93, 1.25, and 1.27, respectively, and C\text{max} ratios of 1.65, 1.46, 1.33, and 1.67, respectively. These results were all reflected in the labels (FDA, 2015a,i,j,za). Interestingly, the largest effect was observed with flibanserin (digoxin AUC ratio = 1.93, C\text{max} ratio = 1.46), although inhibition of P-gp in vitro was quite weak, reducing the eflluX ratio of digoxin from 8.15 to only 3.44 at the highest concentration tested. For the remaining two NMEs (alectinib and uridine triacetate), although one or both of the [I]/IC\text{50} values exceeded the FDA cut-off value, no clinical studies were performed. In the case of prodrug uridine triacetate, which is rapidly converted to uridine (no inhibition of P-gp in vitro) due to the high gut concentrations of uridine triacetate (approximately 37 mM), the sponsor acknowledged that an interaction at the gut level cannot be ruled out; however, no in vivo P-gp inhibition study was conducted.

Finally, two clinical trials were performed to assess whether lesinurad was an in vivo inhibitor of OAT1/3 or OCT1 since in vitro lesinurad inhibited all three transporters with IC\text{50} values < 5 \mu M. To investigate the inhibition potential of OAT1/3, lesinurad (400 mg single dose) was coadministered with furosemide. Although a decrease in furosemide plasma exposure (AUC ratio = 0.69, C\text{max} ratio = 0.49) and a 45% increase in its clearance was observed, the renal clearance was not decreased in the presence of lesinurad. Additionally, there was no effect on the diuretic effects of furosemide; therefore, the sponsor concluded that lesinurad was not an in vivo inhibitor of OAT1/3 (FDA, 2015zg). To investigate OCT1 inhibition, lesinurad was coadministered with metformin and no effect was observed (metformin AUC ratio = 1.03, C\text{max} ratio = 1.06).
sulfasalazine were both >2. As in the previous 2 years, while a majority of the NMEs tested were shown to be either substrates or inhibitors of one or more transporter in vitro, this often failed to translate into positive in vivo interactions, indicative of the need for more research into transporter in vitro to in vivo extrapolation.

**PGx Studies**

For eight NMEs (brexpiprazole, cariprazine, edoxaban, eluxadoline, flibanserin, lenvatinib, lesinurad, and panobinostat), the effects of genetic variants of the primary enzymes (including CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, and CYP3A5) and transporter (OATP1B1) on the PK of each drug were evaluated. This is a significant increase compared with four NMEs in 2014 and two NMEs in 2013 (Yu et al., 2014, 2016). Three NMEs, brexpiprazole, flibanserin, and lesinurad, had PGx study results highlighted in the labeling. Brexpiprazole, which is metabolized by both CYP3A4A (47%) and CYP2D6 (43%), displayed a significant effect of CYP2D6 polymorphism on its disposition. Indeed, the brexpiprazole AUC was about 2-fold higher in CYP2D6 poor metabolizers (PMs) compared with EMs and intermediate metabolizers. In addition, concurrent administration of the strong CYP3A4A inhibitor ketoconazole (200 mg orally once daily) increased brexpiprazole exposure to a similar level in CYP2D6 EMs and intermediate metabolizers (ketoconazole AUC ratio = 2.11), compared with coadministration of ritonavir (400 mg orally once daily; AUC ratio = 4.61, Cmax ratio = 2.11), resulting in a larger change in flibanserin exposure (AUC ratio = 6.41, Cmax = 2.11). Compared with administration of ketoconazole (400 mg orally once daily; AUC ratio = 4.61, Cmax ratio = 1.84), a strong CYP3A4A inhibitor. Based on the interaction study results with flibanserin the label suggests to “discuss the use of a strong CYP2C19 inhibitor with the patients when prescribing flibanserin” (FDA, 2015a).

In contrast, no significant changes in flibanserin PK were observed in CYP2C9 PM or CYP2D6 PM/intermediate metabolizer/ultrarapid metabolizer subjects compared with EMs, indicating minimal involvement of these enzymes in flibanserin metabolism. As for lesinurad, which is primarily metabolized by CYP2C9, a PGx study showed that subjects with a CYP2C9 PM status (i.e., CYP2C9*3/*3) who received lesinurad had an approximately 1.8-fold increase in lesinurad exposure relative to CYP2C9 EMs (i.e., CYP2C9*1/*1). It is recommended that lesinurad be used with caution in CYP2C9 PMs, and in patients taking moderate inhibitors of CYP2C9 (FDA, 2015g).

**PBPK Modeling and Simulations**

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

Cobimetinib, panobinostat, and sonidegib are all extensively metabolized by CYP3A. For these three drugs, the effect of strong inhibition of CYP3A on their plasma exposure was investigated clinically with...
TABLE 8
Clinically significant inhibitions, NMEs as victims or perpetrators

<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Dose</th>
<th>Inhibitor</th>
<th>Enzyme/Transporter Possibly Involved</th>
<th>Ratio</th>
<th>Study Design/Population</th>
<th>Labeling Impact</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC</td>
<td>Cmax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDIs with AUC ratio ≥ 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Josamycin</td>
<td>CYP3A4</td>
<td>7.70</td>
<td>3.60</td>
<td>N/P</td>
<td>Contraindication with strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Ivabradine&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Ketaconazole (200 mg once daily)</td>
<td>CYP3A4, P-gp</td>
<td>7.70</td>
<td>3.60</td>
<td>N/P</td>
<td>Contraindication with strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Cobimetinib (10 mg SD)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Itraconazole (200 mg once daily for 14 days)</td>
<td>CYP3A4, P-gp</td>
<td>6.62</td>
<td>3.17</td>
<td>One-sequence/15 healthy subjects</td>
<td>Avoid CYP3A4 strong inhibitors</td>
</tr>
<tr>
<td>Filbanserin (100 mg SD)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>Fluconazole (200 mg once daily for 6 days)</td>
<td>CYP3A4, CYP2C19 (minor)</td>
<td>6.41</td>
<td>2.11</td>
<td>One-sequence/15 healthy females</td>
<td>Contraindication with CYP3A4 moderate inhibitors</td>
</tr>
<tr>
<td>Isavuconazonium sulfate (200 mg SD)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td></td>
<td>Ketaconazole (200 mg twice daily for 24 days)</td>
<td>CYP3A</td>
<td>5.22</td>
<td>1.09</td>
<td>N/P</td>
<td>Contraindication with strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Filbanserin (50 mg SD)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>Ketaconazole (400 mg once daily for 5 days)</td>
<td>CYP3A4, CYP2C8/9 (minor)</td>
<td>4.61</td>
<td>1.84</td>
<td>Random crossover/20 healthy females</td>
<td>Contraindication with CYP3A4 moderate inhibitors</td>
</tr>
<tr>
<td>Cobimetinib (60 mg once daily for 35 days)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>Erythromycin (500 mg three times daily for 35 days)</td>
<td>CYP3A4, P-gp</td>
<td>4.27</td>
<td>3.76 (PBPK)</td>
<td>PBPK modeling/simulations of healthy subjects</td>
<td>Avoid CYP3A moderate inhibitors</td>
</tr>
<tr>
<td>Eluxadoline (100 mg SD)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>Cyclosporine (600 mg SD)</td>
<td>OATP1B1, MRP2 (minimal)</td>
<td>4.20</td>
<td>6.81</td>
<td>Random crossover/30 healthy subjects</td>
<td>Reduce dose with OATP1B1 inhibitors; monitor for adverse reactions</td>
</tr>
<tr>
<td>Cariprazine (0.5 mg once daily for 14 days)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>Ketaconazole (400 mg)</td>
<td>CYP3A4</td>
<td>3.78</td>
<td>3.27</td>
<td>One-sequence/26 subjects (CYP2D6 EMs and IMs)</td>
<td>Contraindication with CYP3A strong inhibitors</td>
</tr>
<tr>
<td>Dextromethorphan (30 mg SD)</td>
<td></td>
<td>Rolipitant (200 mg SD)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>CYP2D6</td>
<td>3.33</td>
<td>2.77</td>
<td>One-sequence/26 subjects (CYP2D6 EMs and IMs)</td>
<td>Monitor for adverse reactions if concomitant use with other CYP2D6 substrates with a NTI cannot be avoided</td>
</tr>
<tr>
<td>Cobimetinib (60 mg SD)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>Diltiazem (1200 mg twice daily)</td>
<td>CYP3A4, P-gp</td>
<td>3.26</td>
<td>1.85 (PBPK)</td>
<td>PBPK modeling/simulations of healthy subjects</td>
<td>Avoid CYP3A moderate inhibitors</td>
</tr>
<tr>
<td>Daclatasvir (10 mg SD)&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td>Ketaconazole (400 mg once daily for 9 days)</td>
<td>CYP3A4, CYP2C8 (minor)</td>
<td>3.01</td>
<td>1.57</td>
<td>One-sequence/13 healthy subjects</td>
<td>Reduce dose with CYP3A sensitive substrates or CYP2D6 substrates with a NTI</td>
</tr>
<tr>
<td>Ivabradine&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Diltiazem (120 mg twice daily)</td>
<td>CYP3A4, P-gp</td>
<td>3.00</td>
<td>2.50</td>
<td>N/P</td>
<td>Contraindication with strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Dextromethorphan (60 mg SD)</td>
<td></td>
<td>Panobinostat (20 mg once daily for 3 days)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>CYP2D6</td>
<td>2.30</td>
<td>3.00 (PBPK)</td>
<td>One-sequence/14 patients (CYP2D6 EMs)</td>
<td>Avoid long-term use of CYP3A moderate inhibitors</td>
</tr>
<tr>
<td>Sonidegib (200 mg once daily at steady state)&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td>Erythromycin (500 mg once daily for 120 days)</td>
<td>CYP3A</td>
<td>2.80</td>
<td>2.40 (PBPK)</td>
<td>PBPK modeling/simulations of patients</td>
<td>Avoid long-term use of CYP3A moderate inhibitors</td>
</tr>
<tr>
<td>Rocuronium&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td>Sugammadex (4 mg/kg SD)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Not by P450s</td>
<td>2.70</td>
<td>N/P</td>
<td>Parallel/2</td>
<td>Adjust dose</td>
</tr>
<tr>
<td>Tenofovir alafenamide fumarate (8 mg once daily for 22 days)&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td>Cobicistat (150 mg once daily for 10 days)</td>
<td>P-gp, BCRP, OATP1B1, OATP1B3</td>
<td>2.65</td>
<td>2.83</td>
<td>One-sequence/12 healthy subjects</td>
<td>Combination drug</td>
</tr>
<tr>
<td>Filbanserin (50 mg SD)&lt;sup&gt;l&lt;/sup&gt;</td>
<td></td>
<td>Itraconazole (200 mg once daily for 7 days)</td>
<td>CYP3A4, CYP2C8/9 (minor)</td>
<td>2.58</td>
<td>1.70</td>
<td>Random crossover/12 healthy subjects</td>
<td>Contraindication with CYP3A4 strong inhibitors</td>
</tr>
<tr>
<td>Sonidegib (800 mg SD)&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
<td>Ketaconazole (200 mg twice daily for 14 days)</td>
<td>CYP3A</td>
<td>2.26</td>
<td>1.50</td>
<td>Parallel/15 healthy subjects</td>
<td>Avoid CYP3A4 strong inhibitors</td>
</tr>
<tr>
<td>Tacrolimus (5 mg SD)</td>
<td></td>
<td>Isavuconazonium sulfate&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CYP3A4</td>
<td>2.25</td>
<td>1.42</td>
<td>N/P</td>
<td>Caution; adjust immunosuppressant’s dose as needed</td>
</tr>
<tr>
<td>Daclatasvir (60 mg once daily for 7 days)&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
<td>Simeprevir (150 mg once daily for 7 days)</td>
<td>CYP3A, P-gp</td>
<td>2.20</td>
<td>1.60</td>
<td>Random crossover/15 healthy nonsmokers</td>
<td>Reduce dose when it is coadministered with simprevir&lt;sup&gt;E&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Inhibitor</th>
<th>Enzyme/Transporter Possibly Involved</th>
<th>Ratio</th>
<th>Study Design/Population</th>
<th>Labeling Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Grapefruit juice</td>
<td>CYP3A4</td>
<td>2.20</td>
<td>Cmax</td>
<td>N/P</td>
<td>Avoid concomitant use of moderate CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Sulfasalazine (500 mg SD)</td>
<td>Rolipitant (200 mg SD)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>BCRP</td>
<td>2.18</td>
<td>Cmax</td>
<td>One-sequence/20</td>
<td>Monitor for adverse events</td>
</tr>
<tr>
<td>Brexpiprazole (2 mg SD)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Ketoconazole (200 mg twice daily for 7 days)</td>
<td>CYP3A4, CYP2D6</td>
<td>2.17</td>
<td>Cmax</td>
<td>One-sequence/12 healthy subjects (CYP2D6 EMs and IMs)</td>
<td>Reduce dose with CYP3A4 strong inhibitors</td>
</tr>
<tr>
<td>Daclatasvir (60 mg once daily for 7 days)</td>
<td>Atazanavir/ritonavir (300 mg/100 mg once daily for 10 days)</td>
<td>CYP3A</td>
<td>2.10</td>
<td>Cmax</td>
<td>One-sequence/14 healthy subjects</td>
<td>Reduce dose with CYP3A4 strong inhibitors</td>
</tr>
<tr>
<td>Midazolam (3 mg SD)</td>
<td>Isavuconazonium sulfate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>CYP3A4, CYP2D6</td>
<td>2.03 (EMs)</td>
<td>Cmax</td>
<td>One-sequence/11 healthy subjects (CYP2D6 EMs and IMs)</td>
<td>Caution; reduce dose</td>
</tr>
<tr>
<td>Brexpiprazole (2 mg SD)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Quinidine (324 mg once daily for 7 days)</td>
<td>CYP3A4</td>
<td>2.00</td>
<td>Cmax</td>
<td>None</td>
<td>Avoid concomitant use with moderate CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Simeprevir&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Lopinavir and ritonavir</td>
<td>P-gp, OATP1B1, OATP1B3</td>
<td>2.00</td>
<td>Cmax</td>
<td>N/P</td>
<td>Caution with lopinavir/ritonavir, monitor for toxicity by isavuconazole</td>
</tr>
<tr>
<td>Midazolam (2 mg SD)</td>
<td>Isavuconazonium sulfate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>CYP3A</td>
<td>1.96</td>
<td>Cmax</td>
<td>Random crossover/23 healthy subjects</td>
<td>Increase monitoring of digoxin concentrations</td>
</tr>
<tr>
<td>Digoxin (0.5 mg SD)</td>
<td>Fibanserin (100 mg once daily for 8 days)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>P-gp</td>
<td>1.93</td>
<td>Cmax</td>
<td>N/P</td>
<td>Reduce dose with P-gp inhibitors</td>
</tr>
<tr>
<td>Edoxaban (60 mg SD)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Ketoconazole (400 mg once daily for 7 days)</td>
<td>P-gp</td>
<td>1.87</td>
<td>Cmax</td>
<td>N/P</td>
<td>Reduce dose with P-gp inhibitors</td>
</tr>
<tr>
<td>Edoxaban (60 mg SD)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Erythromycin (500 mg four times daily for 8 days)</td>
<td>P-gp</td>
<td>1.85</td>
<td>Cmax</td>
<td>N/P</td>
<td>Reduce dose with P-gp inhibitors</td>
</tr>
<tr>
<td>Palbociclib (125 mg SD)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Itraconazole (200 mg once daily for 11 days)</td>
<td>CYP3A</td>
<td>1.85</td>
<td>Cmax</td>
<td>One-sequence/11 healthy subjects</td>
<td>Avoid CYP3A strong inhibitors</td>
</tr>
<tr>
<td>Edoxaban (60 mg SD)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dronedarone (400 mg twice daily)</td>
<td>P-gp</td>
<td>1.84</td>
<td>Cmax</td>
<td>N/P</td>
<td>Reduce dose with P-gp inhibitors</td>
</tr>
<tr>
<td>Sirolimus (2 mg SD)</td>
<td>Isavuconazonium sulfate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>CYP3A4</td>
<td>1.84</td>
<td>Cmax</td>
<td>N/P</td>
<td>Caution; adjust immunosuppressant’s dose as needed</td>
</tr>
<tr>
<td>Edoxaban (60 mg SD)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Quinidine (300 mg three times daily)</td>
<td>P-gp</td>
<td>1.75</td>
<td>Cmax</td>
<td>N/P</td>
<td>Reduce dose with P-gp inhibitors</td>
</tr>
<tr>
<td>Edoxaban (60 mg SD)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cyclosporine (500 mg SD)</td>
<td>P-gp, OATP1B1 (metabolite M4)</td>
<td>1.73 (metabolite M4: 6.87)</td>
<td>Cmax</td>
<td>N/P</td>
<td>Reduce dose with P-gp inhibitors</td>
</tr>
<tr>
<td>Trabectedin (1.3 mg/m2 SD (alone); 0.58 mg/m2 (coadministration))&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Ketoconazole (200 mg twice daily × 15 doses)</td>
<td>CYP3A4</td>
<td>1.69</td>
<td>Cmax</td>
<td>Random crossover/8 patients</td>
<td>Avoid strong CYP3A inhibitors</td>
</tr>
<tr>
<td>Midazolam (2 mg SD)</td>
<td>Palbociclib (125 mg once daily for 8 days)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CYP3A</td>
<td>1.58</td>
<td>Cmax</td>
<td>Random crossover/26 healthy females</td>
<td>Reduce dose with sensitive CYP3A substrates with a NTI</td>
</tr>
<tr>
<td>Lesinurad (400 mg SD)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Flaconazole (400 mg loading dose + 200 mg once daily for 2 days)</td>
<td>CYP2C9</td>
<td>1.54</td>
<td>Cmax</td>
<td>One-sequence/12 healthy males</td>
<td>Caution with moderate CYP2C9 inhibitors</td>
</tr>
<tr>
<td>Simeprevir (150 mg once daily for 7 days)</td>
<td>Daclatasvir (60 mg once daily for 7 days)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CYP3A, OATP1B1, OATP1B3</td>
<td>1.51</td>
<td>Cmax</td>
<td>Random crossover/24 healthy nonsmokers</td>
<td>Reduce dose when coadministered with simeprevir&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Dose</th>
<th>Inhibitor</th>
<th>Enzyme/Transporter Possibly Involved</th>
<th>Ratio</th>
<th>Study Design/Population</th>
<th>Labeling Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodusavatin (10 mg SD)</td>
<td>Daclatasvir (60 mg once daily for 9 days)</td>
<td>CYP3A, BCRP, OTATP1B1, OATP1B3</td>
<td>AUC 1.47, Cmax 1.84 One-sequence/21 healthy subjects</td>
<td></td>
<td>Monitor for adverse events</td>
<td>FDA (2015j)</td>
<td></td>
</tr>
<tr>
<td>Flibanserin (25–100 mg SD)</td>
<td>Oral contraceptives</td>
<td>CYP3A4, CYP2C19 (minor)</td>
<td>AUC 1.42, Cmax 1.12 N/P/39 healthy female subjects and patients</td>
<td></td>
<td>Oral contraceptives and other weak CYP3A4 inhibitors may increase flibanserin exposures and incidence of adverse reactions</td>
<td>FDA (2015a)</td>
<td></td>
</tr>
<tr>
<td>Panobinostat (20 mg SD)</td>
<td>Ketoconazole (400 mg once daily for 5 days)</td>
<td>CYP3A, P-gp</td>
<td>AUC 1.66, Cmax 1.62 One-sequence/14 patients</td>
<td></td>
<td>Reduce dose with strong CYP3A4 inhibitors</td>
<td>FDA (2015l)</td>
<td></td>
</tr>
<tr>
<td>Panobinostat (25 mg 3 times a week for 3 weeks)</td>
<td>Bortezomib (1.3 mg/m² twice a week for 2 weeks)</td>
<td>CYP3A</td>
<td>AUC 1.42, Cmax 1.50 One-sequence/7 patients</td>
<td></td>
<td>Reduce dose with strong CYP3A inhibitors</td>
<td>FDA (2015l)</td>
<td></td>
</tr>
<tr>
<td>Rodusavatin (20 mg SD)</td>
<td>Eluxadoline (100 mg SD)</td>
<td>OATP1B1</td>
<td>AUC 1.41, Cmax 1.18 Random crossover/27 healthy subjects</td>
<td></td>
<td>Reduce dose of rodusavatin; caution for an increased risk of myopathy/ rhabdomyolysis</td>
<td>FDA (2015zc)</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (20 mg SD)</td>
<td>Isavuconazonium sulfate</td>
<td>CYP3A4</td>
<td>AUC 1.40, Cmax 1.05 N/P</td>
<td></td>
<td>Caution; monitor for adverse reactions</td>
<td>FDA (2015i)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (60 mg SD)</td>
<td>Amisdrone (400 mg once daily for 4 days)</td>
<td>P-gp</td>
<td>AUC 1.40, Cmax 1.60 N/P</td>
<td></td>
<td>Reduce dose with P-gp inhibitors</td>
<td>FDA (2015w)</td>
<td></td>
</tr>
<tr>
<td>Mycophenylate mofetil (1 g SD)</td>
<td>Isavuconazonium sulfate (200 mg once daily)</td>
<td>UGTs</td>
<td>AUC 1.35, Cmax 0.89 N/P</td>
<td></td>
<td>Caution; monitor for toxicity</td>
<td>FDA (2015i)</td>
<td></td>
</tr>
<tr>
<td>Flibanserin (100 mg SD)</td>
<td>Grapefruit juice (240 ml regular strength SD)</td>
<td>CYP3A4</td>
<td>AUC 1.34, Cmax 1.07 One-sequence/26 healthy females</td>
<td></td>
<td>Contraindication with CYP3A4 moderate inhibitors</td>
<td>FDA (2015a)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (300 mg SD)</td>
<td>Isavuconazonium sulfate</td>
<td>CYP3A4</td>
<td>AUC 1.30, Cmax 1.10 N/P</td>
<td></td>
<td>Caution; monitor cyclosporine concentrations and adjust dose as needed</td>
<td>FDA (2015i)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (60 mg once daily for 5 days)</td>
<td>Acetylsalicylic acid (325 mg once daily for 5 days)</td>
<td>NP</td>
<td>AUC 1.30, Cmax 1.30 N/P/healthy volunteers</td>
<td></td>
<td>Monitor for bleeding</td>
<td>FDA (2015w)</td>
<td></td>
</tr>
<tr>
<td>Digoxin (0.125 mg once daily for 20 days)</td>
<td>Daclatasvir (60 mg once daily for 10 days)</td>
<td>P-gp</td>
<td>AUC 1.27, Cmax 1.65 One-sequence/15 healthy subjects</td>
<td></td>
<td>Monitor digoxin concentrations; adjust digoxin doses if necessary</td>
<td>FDA (2015j)</td>
<td></td>
</tr>
<tr>
<td>Digoxin (0.5 mg SD)</td>
<td>Rolapitant (180 mg SD)</td>
<td>P-gp</td>
<td>AUC 1.27, Cmax 1.67 One-sequence/16</td>
<td></td>
<td>Monitor for adverse reactions for concomitant use of P-gp substrates with a NTI</td>
<td>FDA (2015za)</td>
<td></td>
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<tr>
<td>Digoxin (0.5 mg SD)</td>
<td>Isavuconazonium sulfate (200 mg once daily)</td>
<td>P-gp</td>
<td>AUC 1.25, Cmax 1.33 N/P</td>
<td></td>
<td>Adjust dose for P-gp substrates with a NTI; monitor serum digoxin concentrations</td>
<td>FDA (2015i)</td>
<td></td>
</tr>
</tbody>
</table>

*IM, intermediate metabolizer; N/P, not provided; SD, single dose.

1 The number of subjects listed represents the number of subjects who completed both treatments, as described in the University of Washington Drug Interaction Database.
2 For victim exposure.
3 NMEs in 2015.
4 Isavuconazonium sulfate was measured.
5 Large variabilities were observed; maximum values were obtained from the product label.
6 Drug was given intravenously.
7 Labeling recommendations were extracted from clinical pharmacology and biopharmaceutics reviews.
8 For victim exposure with dose recommendation.
<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Dose</th>
<th>Inducer</th>
<th>Main Enzyme/Transporter Possibly Involved</th>
<th>Ratio</th>
<th>Study Design/Population</th>
<th>Labeling Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isavuconazonium sulfate</td>
<td>Rifampin (600 mg once daily)</td>
<td>CYP3A</td>
<td>0.03</td>
<td>0.25</td>
<td>N/P</td>
<td>Contraindication with strong CYP3A4 inducers</td>
<td>FDA (2015i)</td>
</tr>
<tr>
<td>Flibanserin (100 mg SD)</td>
<td>Rifampin (600 mg once daily for 9 days)</td>
<td>CYP3A4, CYP2C19 (minor)</td>
<td>0.04</td>
<td>0.10</td>
<td>Random crossover/23 healthy females</td>
<td>FDA (2015a)</td>
<td></td>
</tr>
<tr>
<td>Rolapitant (200 mg SD)</td>
<td>Rifampin (600 mg once daily for 14 days)</td>
<td>CYP3A4</td>
<td>0.12</td>
<td>0.68</td>
<td>One-sequence/20 healthy subjects</td>
<td>Avoid CYP3A strong inducers</td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>Palbociclib (125 mg SD)</td>
<td>Rifampin (600 mg once daily for 12 days)</td>
<td>CYP3A</td>
<td>0.15</td>
<td>0.28</td>
<td>One-sequence/14 healthy subjects</td>
<td>Avoid moderate and strong CYP3A inducers</td>
<td>FDA (2015n)</td>
</tr>
<tr>
<td>Cobimetinib (60 mg SD)</td>
<td>Rifampin (600 mg once daily)</td>
<td>CYP3A4, P-gp</td>
<td>0.17 (PBPK) 0.37 (PBPK)</td>
<td>PBPK modeling/simulations of healthy subjects</td>
<td>Avoid CYP3A strong inducers</td>
<td>FDA (2015h)</td>
<td></td>
</tr>
<tr>
<td>Ivacatad</td>
<td>Lamacatad</td>
<td>CYP3A</td>
<td>0.20</td>
<td>N/P</td>
<td>N/P</td>
<td>Coadministration with strong CYP3A inducers is not recommended</td>
<td>FDA (2015u)</td>
</tr>
<tr>
<td>Daclatasvir (60 mg SD)</td>
<td>Rifampin (600 mg once daily for 9 days)</td>
<td>CYP3A, CYP2C8 (minor), P-gp</td>
<td>0.21</td>
<td>0.44</td>
<td>One-sequence/14 healthy Asian Males</td>
<td>Increase dose with CYP3A strong inducers</td>
<td>FDA (2015j)</td>
</tr>
<tr>
<td>Brexpiprazole (4 mg SD)</td>
<td>Rifampin (600 mg once daily for 13 days)</td>
<td>CYP3A4</td>
<td>0.24</td>
<td>0.69</td>
<td>One-sequence/16 healthy subjects</td>
<td>None</td>
<td>FDA (2015b)</td>
</tr>
<tr>
<td>Ixazomib citrate (4 mg SD)</td>
<td>Rifampin (600 mg once daily for 14 days)</td>
<td>CYP3A</td>
<td>0.26</td>
<td>0.46</td>
<td>Parallel/16 patients</td>
<td>Avoid CYP3A strong inducers</td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td>Cobimetinib (60 mg once daily for 21 days)</td>
<td>Efavirenz (600 mg once daily for 21 days)</td>
<td>CYP3A4, P-gp</td>
<td>0.27 (PBPK) 0.29 (PBPK)</td>
<td>PBPK modeling/simulations of healthy subjects</td>
<td>Avoid CYP3A moderate inducers</td>
<td>FDA (2015h)</td>
<td></td>
</tr>
<tr>
<td>Alectinib (600 mg SD)</td>
<td>Rifampin (600 mg once daily for 13 days)</td>
<td>CYP3A</td>
<td>0.27</td>
<td>0.49</td>
<td>One-sequence/24 healthy subjects</td>
<td>None</td>
<td>FDA (2015b)</td>
</tr>
<tr>
<td>Sonidegib (800 mg SD)</td>
<td>Rifampin (600 mg once daily for 14 days)</td>
<td>CYP3A</td>
<td>0.28</td>
<td>0.46</td>
<td>Parallel/16 healthy subjects</td>
<td>Avoid CYP3A strong inducers</td>
<td>FDA (2015d)</td>
</tr>
<tr>
<td>Sonidegib (200 mg once daily at steady state)</td>
<td>Efavirenz (600 mg once daily for 120 days)</td>
<td>CYP3A</td>
<td>0.31 (PBPK) 0.4 (PBPK)</td>
<td>PBPK modeling/simulations of patients</td>
<td>Avoid CYP3A moderate inducers</td>
<td>FDA (2015d)</td>
<td></td>
</tr>
<tr>
<td>Palbociclib (125 mg SD)</td>
<td>Rifampin (600 mg once daily for 14 days)</td>
<td>CYP3A4, P-gp</td>
<td>0.35 (PBPK) 0.43 (PBPK)</td>
<td>PBPK modeling/simulations of 10 trials of 10 healthy subjects</td>
<td>Avoid CYP3A strong inducers</td>
<td>FDA (2015d)</td>
<td></td>
</tr>
<tr>
<td>Ivalratadine</td>
<td>St. John’s Wort extract</td>
<td>CYP3A4, P-gp</td>
<td>0.40</td>
<td>0.50</td>
<td>N/P</td>
<td>Avoid concomitant use of CYP3A4 inducers</td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>DDIIs with 0.8 &lt; AUC ratio ≤ 0.5</td>
<td>Trabectedin (1.3 mg/m² SD)</td>
<td>Rifampin (600 mg once daily for 6 days)</td>
<td>CYP3A4, P-gp</td>
<td>0.55</td>
<td>0.77</td>
<td>Random crossover/8 patients</td>
<td>Avoid CYP3A strong inducers</td>
</tr>
<tr>
<td></td>
<td>Amlodipine (5 mg once daily for 28 days)</td>
<td>Lesinurad (400 mg once daily)</td>
<td>CYP3A</td>
<td>0.58</td>
<td>0.61</td>
<td>One-sequence/13 healthy males</td>
<td>Monitor for a potential reduction in efficacy of sensitive CYP3A substrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lesinurad (400 mg SD)</td>
<td>CYP2B6</td>
<td>0.58</td>
<td>0.69</td>
<td>N/P</td>
<td>Caution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lesinurad and allopurinol (300 mg/200 mg once daily for 10 days)</td>
<td>CYP3A</td>
<td>0.66</td>
<td>0.66</td>
<td>Random crossover/12 healthy males</td>
<td>Monitor for potential reduction in efficacy during concomitant use with moderate CYP2C9 inducer</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Enzyme/Transporter</th>
<th>Ratio</th>
<th>Study Design/Population</th>
<th>Labeling Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir (60 mg once daily for 14 days) and ritonavir (100 mg twice daily)</td>
<td>CYP3A, P-gp</td>
<td>0.68</td>
<td>One-sequence/17 healthy subjects</td>
<td>Increase dose with CYP3A moderate inducers</td>
<td>FDA (2015j)</td>
</tr>
<tr>
<td>Isavuconazonium sulfate (120 mg once daily for 5 days) and lopinavir (400 mg twice daily)</td>
<td>CYP3A</td>
<td>0.69</td>
<td>Not provided</td>
<td>N/P</td>
<td>Caution</td>
</tr>
<tr>
<td>Etravirine (200 mg twice daily for 15 days) and panobinostat (100 mg SD)</td>
<td>CYP3A4</td>
<td>0.75</td>
<td>One-sequence/24 healthy subjects</td>
<td>CYP3A4 inducers not recommended</td>
<td>FDA (2015a)</td>
</tr>
</tbody>
</table>

N/P, not provided; SD, single dose.

a The number of subjects listed represents the number of subjects who completed both treatments, as described in the University of Washington Drug Interaction Database.

b For victim exposure.
c NMEs in 2015.
e Drug was given intravenously.

PBPK modeling results were used to support dosing recommendations as an alternative for clinical studies. For example, for cobimetinib, it was predicted that coadministration with the strong inducer rifampin (600 mg orally once daily) or moderate inducer efavirenz (600 mg orally once daily) may decrease cobimetinib exposure by 83% and 73%, respectively. Due to the possibility of reduced efficacy of cobimetinib, the product label recommends avoiding concomitant administration with both strong and moderate inducers of CYP3A (FDA, 2015h). On the other hand, coadministration of cobimetinib with the moderate CYP3A inhibitors erythromycin (500 mg orally three times daily) or diltiazem (1200 mg orally twice daily) was predicted to cause a 3- to 4-fold increase in cobimetinib exposure, whereas coadministration of fluvoxamine, a weak inhibitor of CYP3A, was predicted to have no effect on cobimetinib plasma levels. Consequently, it is recommended to avoid concomitant use of cobimetinib with strong or moderate CYP3A inhibitors (FDA, 2015i).

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

**Clinically Significant DDIs**

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

For inhibition studies, a total of 68 DDI evaluations (including three PBPK simulations) showed an exposure change of more than 25% of the substrate, with NMEs being victims or inhibitors. Among them, about 80% of the results were reflected in the labeling, one-half of which had \( \frac{AUC}{AUC} \) ratios of 2, and one-half with \( \frac{AUC}{AUC} \) ratios of 1.25 to 2. A majority of the NMEs (\( n = 18 \)) were victims, whereas nine NMEs were perpetrators, with seven NMEs being both. Two-thirds of the clinical interactions were due to inhibition of CYP3A. Of note, one-half of the NMEs that were CYP3A substrates were also transported by P-gp and/or BCRP; therefore, inhibition of these transporters may also contribute to the overall observed interactions. Other P450 enzymes, such as CYP2C9, CYP2C19, and CYP2D6 were also sensitive substrates of CYP3A. Almost one-half of the observed clinical interactions were mediated primarily by inhibition of transporters, including P-gp, BCRP, and OATP1B1/3. Several NMEs were also found to inhibit both enzymes and transporters. For example, isavuconazole (administered as the prodrug isavuconazonium sulfate) inhibited CYP3A (midazolam \( \frac{AUC}{AUC} \) ratio = 2.03, \( C_{max} \) ratio = 1.72), UGTs (mycophenylate mofetil \( \frac{AUC}{AUC} \) ratio = 1.35, \( C_{max} \) ratio = 0.89), and P-gp (digoxin \( \frac{AUC}{AUC} \) ratio = 1.25, \( C_{max} \) ratio = 1.33).

### TABLE 10

NMEs with HI-related labeling impact

The \( AUC \) and \( C_{max} \) ratios presented were calculated by the University of Washington Drug Interaction Database editorial team using mean \( AUC \) and \( C_{max} \) values available in the NDA review documents and may differ from those presented in the product label.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Maximal AUC</th>
<th>( C_{max} ) Ratio</th>
<th>Labeling Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eluxadoline</td>
<td>13.74 (severe)</td>
<td>14.25 (severe)</td>
<td>Reduce dose (mild and moderate); contraindication (severe)</td>
<td>FDA (2015zc)</td>
</tr>
<tr>
<td>Fibanserin</td>
<td>4.53 (mild)</td>
<td>0.91 (mild)</td>
<td>Contraindication (any HI)</td>
<td>FDA (2015a)</td>
</tr>
<tr>
<td>Lenvatin</td>
<td>2.57 (severe)</td>
<td>0.54 (severe)</td>
<td>Reduce dose (severe)</td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Isavuconazonium Sulfate</td>
<td>Isavuconazole: 2.19 (moderate)</td>
<td>Isavuconazole: 0.77 (moderate)</td>
<td>Not recommended (severe)</td>
<td>FDA (2015i)</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>2.05 (moderate)</td>
<td>1.83 (moderate)</td>
<td>Reduce dose (mild and moderate); avoid use (severe)</td>
<td>FDA (2015l)</td>
</tr>
<tr>
<td>Selexipag</td>
<td>4 (moderate); ACT-333679: 2 (moderate)</td>
<td>N/P</td>
<td>Avoid use (severe)</td>
<td>FDA (2015z)</td>
</tr>
<tr>
<td>Sacubitril</td>
<td>3.45 (moderate); LBQ657: 1.9 (moderate)</td>
<td>N/P</td>
<td>Reduce dose (moderate); not recommended (severe)</td>
<td>FDA (2015k)</td>
</tr>
<tr>
<td>Lumacator</td>
<td>1.50 (moderate)</td>
<td>1.30 (moderate)</td>
<td>Reduce dose (moderate and severe)</td>
<td>FDA (2015u)</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>1.46 (moderate)</td>
<td>0.76 (moderate)</td>
<td>Reduce dose (moderate and severe)</td>
<td>FDA (2015v)</td>
</tr>
<tr>
<td>Lesinurad</td>
<td>1.33 (moderate)</td>
<td>1.08 (moderate)</td>
<td>Not recommended (severe)</td>
<td>FDA (2015g)</td>
</tr>
<tr>
<td>Ixazomib citrate</td>
<td>Ixazomib: 1.27 (moderate)</td>
<td>Ixazomib: 1.21 (moderate)</td>
<td>Reduce dose (moderate, severe)</td>
<td>FDA (2015s)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.95 (mild); metabolite M4: 1.25 (mild)</td>
<td>0.9 (mild); metabolite M4: 1.1 (mild)</td>
<td>Not recommended (moderate and severe)</td>
<td>FDA (2015w)</td>
</tr>
<tr>
<td>AUC ratio &lt; 1.25b</td>
<td>1.04 (moderate)</td>
<td>0.77 (moderate)</td>
<td>Avoid use (severe)</td>
<td>FDA (2015za)</td>
</tr>
<tr>
<td>Rolapitant</td>
<td>1.15 (moderate)</td>
<td>1.14 (moderate)</td>
<td>Not recommended (severe)</td>
<td>FDA (2015zd)</td>
</tr>
<tr>
<td>Tenofurin alafenamide fumarate</td>
<td>0.92 (mild); tenofovir: 0.89 (mild)</td>
<td>N/P</td>
<td>Not recommended (severe)</td>
<td>FDA (2015m)</td>
</tr>
<tr>
<td>No dedicated HI study b</td>
<td>N/P</td>
<td>N/P</td>
<td>Contraindication (severe)</td>
<td>FDA (2015g)</td>
</tr>
</tbody>
</table>

**PMR Requested**

- Ibavradine
- Rolapitant
- Trabectedin
- Osimertinib
- Alectinib

\( \text{N/P, not provided; N/T, not tested.} \)

\( \text{\#1 The } C_{max} \text{ ratio presented are for the same patient population as the maximal } AUC \text{ ratio.} \)

\( \text{\#2 With dosing recommendation.} \)

\( \text{\#3 Drug was given intravenously.} \)
and nearly all of the results were highlighted in the respective drugs. Substrate exposure that could be explained predominantly by alteration of multiple enzymes and transporters, including P-gp. When NMEs were evaluated as perpetrators, about one-third of the clinical drug interactions were mediated by transporters. The highest exposure change was observed with coadministration of rolapitant (200 mg orally single dose), which increased sulfasalazine AUC by 2.2-fold and Cmax by 6.3-fold, indicating inhibition of intestinal BCRP. Four NMEs, namely, daclatasvir (60 mg orally once daily), flibanserin (100 mg orally once daily), isavuconazole (200 mg orally once daily), and rolupitant (180 mg daily), were found to inhibit P-gp, with increases of 25%–93% in the exposure to the active moiety (selexipag metabolite ACT-333679 and lumacaftor (CYP3A)).

Finally, for transporter-based clinical interactions, there were 19 inhibition interactions with over a 1.25-fold increase in substrate exposure and one induction interaction with more than a 20% decrease in substrate exposure that could be explained predominately by alteration of transport. Four NMEs (edoxaban, eluxadoline, selefixap, and tenofovir alafenamide fumarate) were victims of drug interactions in which transporters were the main contributor to the underlying mechanism. Edoxaban was found to be sensitive to both inhibition of P-gp and OATP1B1 by multiple inhibitors (30%–90% increase in exposure) and induction by rifampin (a 40% decrease in exposure), a known inducer of multiple enzymes and transporters, including P-gp. When NMEs were evaluated as perpetrators, about one-third of the clinical drug interactions were mediated by transporters. The highest exposure change was observed with coadministration of rolapitant (200 mg orally single dose), which increased sulfasalazine AUC by 2.2-fold and Cmax by 6.3-fold, indicating inhibition of intestinal BCRP. Four NMEs, namely, daclatasvir (60 mg orally once daily), flibanserin (100 mg orally once daily), isavuconazole (200 mg orally once daily), and rolupitant (180 mg single dose), were found to inhibit P-gp, with increases of 25%–93% in the exposure to the active moiety (selexipag metabolite ACT-333679 and lumacaftor (CYP3A)).

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

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

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

With regard to RI studies, nine out of the 16 NMEs evaluated showed AUC ratios $\geq$ 1.25 in renally impaired patients versus healthy controls, resulting in specific dosing recommendations, whereas one NME (parathyroid hormone) had AUC ratios < 1.25 still reported dosing recommendations (Table 11). For four NMEs, cariprazine, cholic acid, lumacaftor, and tipiracil, even though dedicated RI studies were not performed, dosing recommendations for patients with RI were provided. In addition, a PMR was requested to evaluate the effects of RI on the PK of eluxadoline. Among the nine NMEs with systemic exposure increased by $\geq$ 1.25-fold, six (avibactam, edoxaban, ixazomib citrate, sacubitril, suksamadexime, and tenofovir alafenamide fumarate) are mainly eliminated via renal excretion, whereas brexpiprazole and nelarabine are mainly eliminated by biliary excretion, and lesinurad is eliminated by both renal and hepatic routes. Avibactam displayed the largest change in exposure in RI patients, with 3.8-, 7.1-, and 20-fold increases in the AUC in moderate, severe, and end-stage renal disease patients, respectively, with dose adjustment recommendations for all RI patients (FDA, 2015d). Other changes in exposure ranged from a 1.4-fold change in ixazomib AUC in patients with severe RI to a 17.2-fold increase in AUC for suksamadexime when administered in patients with severe RI, causing specific labeling recommendations in both cases. Of note, all the results with AUC ratios $\geq$ 1.25 were reflected in the labeling, except for canaglreol, which showed 2.2- and 4.0-fold increases in AUC and C$_{\text{max}}$ values, respectively, in RI patients (creatinine clearance 20–70 ml/min). However, further evaluations in phase III studies found no significant effect of renal function on canaglreol safety and efficacy; therefore, no dose adjustment was needed for the use in RI patients (FDA, 2015a).

Conclusions

The current mechanistic approach used during the drug development process of NMEs to assess the risk of PK-based DDIs provides a solid framework for translating the observed results of preclinical and clinical evaluations into actionable recommendations. Similar to what was observed in previous years, the detailed evaluation of DDI data contained in the 2015 NDAs showed that most of these drugs were extensively evaluated and their drug interaction profiles were well characterized, with a continued effort in transporter-based DDIs and PBPK modeling and simulations. Overall, when considered as victims, three NMEs (cobimetinib, isavuconazole, and ivabradine) were identified as sensitive clinical substrates of CYP3A (with changes in exposure greater than 5-fold when coadministered with a strong inhibitor), whereas as perpetrators most clinical DDIs involved weak-to-moderate inhibition or induction, with only one NME (lumacaftor) considered as a strong CYP3A4 inducer.

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Authorship Contributions

Participated in research design: Yu, Zhou, Owens, Ritchie, Raguenneau-Majlessi. Performed data analysis: Yu, Zhou, Owens, Ritchie, Raguenneau-Majlessi. Wrote or contributed to the writing of the manuscript: Yu, Zhou, Owens, Ritchie, Raguenneau-Majlessi.

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Food and Drug Administration (2015w) Drug approval package: SAVAYSA (edoxaban). FDA application NDA 203314, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015x) Drug approval package: TRESIBA (insulin delgudec). FDA application NDA 207947, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015y) Drug approval package: UPTRAVI (selexipag). FDA application NDA 207939, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015za) Drug approval package: VARUBI (rolapitant). FDA application NDA 205739, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015zb) Drug approval package: VELTASSA (patiromer). FDA application NDA 205739, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015zc) Drug approval package: VIBERZI (eluxadoline). FDA application NDA 206940, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015zd) Drug approval package: VRAYLAR (cariprazine). FDA application NDA 204370, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015ze) Drug approval package: XURIDEN (uridine triacetate). FDA application NDA 208169, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015zf) Drug approval package: YONDELIS (trabectedin). FDA application NDA 207953, Food and Drug Administration, Silver Spring, MD.

Food and Drug Administration (2015zg) Drug approval package: ZURAMPIC (lesinurad). FDA application NDA 207988, Food and Drug Administration, Silver Spring, MD.


Address correspondence to: Isabelle Ragueneau-Majlessi, Drug Interaction Database Program, Department of Pharmaceutics, University of Washington, Box 357610, Seattle, WA 98195. E-mail: imaj@uw.edu
What Can Be Learned from Recent New Drug and Biologic License Applications? A Systematic Review of Drug Interaction Data for Drugs Approved by the U.S. FDA in 2015

Jingjing Yu, Zhu Zhou, Katie Owens, Tasha K. Ritchie, and Isabelle Ragueneau-Majlessi

Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, WA, USA (J.Y., Z.Z, K.O., T.K.R., I.R-M.)

Drug Metabolism and Disposition

Supplemental Data

Contents:

- Supplemental Table 1
Supplemental Table 1. Chemical structures of compounds within the NDA approved in 2015 (ordered by approval date)

<table>
<thead>
<tr>
<th>NDA (Approval Date)</th>
<th>Compound</th>
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*IVacaftor* (873054-44-5)

*Sacubitril* (149709-62-6)

*Valsartan* (137862-53-4)

*Brexiprazole* (913611-97-9)

*Sonidegib* (956697-53-3)

*Daclatasvir* (1009119-64-5)

*Flibanserin* (167933-07-5)
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<td>Aripiprazole lauroxil</td>
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205739  Patiromer  
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207953  Trabectedin  
(10/23)  
(114899-77-3)

Elvitegravir*  
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207561  Cobicistat*  
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Emtricitabine*  
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Tenofovir alafenamide fumarate (sulfate) (1392275-56-7)

Tenofovir alafenamide fumarate (sulfate)
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*Drugs approved prior to 2015*