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Pharmacokinetic Drug-Drug Interactions with Drugs Approved by the US Food and Drug Administration in 2020: Mechanistic Understanding and Clinical Recommendations[S]

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ABSTRACT

Drug-drug interaction (DDI) data for small molecular drugs approved by the US Food and Drug Administration in 2020 (*N* = 40) were analyzed using the University of Washington Drug Interaction Database. The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the new drug application reviews. About 180 positive clinical studies defined as mean area under the curve ratios (AUCRs) ≥1.25 for inhibition DDIs or pharmacogenetic studies and ≤0.8 for induction DDIs were then fully analyzed. Oncology was the most represented therapeutic area, including 30% of 2020 approvals. As victim drugs, inhibition and induction of CYP3A explained most of all observed clinical interactions. Three sensitive substrates were identified: avapritinib (CYP3A), lonafarnib (CYP3A), and relugolix (P-glycoprotein), with AUCRs of 7.00, 5.07, and 6.25 when coadministered with itraconazole, ketoconazole, and erythromycin, respectively. As precipitants, three drugs were considered strong inhibitors of enzymes (AUCR ≥ 5): cedazuridine for cytidine deaminase and lonafarnib and tucatinib for CYP3A. No drug showed strong inhibition of transporters. No strong inducer of enzymes or transporters was identified. As expected, all DDIs with AUCRs ≥5 or ≤0.2 and almost all those with AUCRs of 2–5 and 0.2–0.5 triggered dosing recommendations in the drug label. Overall, all 2020 drugs found to be either sensitive substrates or strong inhibitors of enzymes or transporters were oncology treatments, underscoring the need for effective DDI management strategies in patients with cancer often receiving polytherapy.

SIGNIFICANCE STATEMENT

This minireview provides a thorough and specific overview of the most significant pharmacokinetic-based DDI data observed (or expected) with small molecular drugs approved by the US Food and Drug Administration in 2020. It will help to better understand mitigation strategies to manage the DDI risks in the clinic.

Introduction

Understanding the various processes involved in pharmacokinetic drug-drug interactions (DDIs) is critical to facilitate the optimal management of these DDIs in the clinic. For over 2 decades, the US Food and Drug Administration (FDA) has released several guidance documents on drug interactions (with the most recent version published last year); 2020 DDI guidance (FDA, 2020r,s) provided a strong framework for the evaluation of DDIs during drug development and identifying essential information to be communicated in labeling to enable the safe and effective use of new marketed products. A systematic, risk-based, integrated approach, including in vitro, in silico, and clinical evaluations, has been recommended by regulators to evaluate enzyme- and transporter-mediated drug interactions. In general, a new drug should be evaluated in vitro, and further clinical evaluations (or in silico predictions, when appropriate) with clinical index inhibitors, inducers, substrates, or likely concomitant medications in the indicated patient populations may be warranted (FDA, 2020r,s). This systematic, mechanistic, and quantitative approach recommended by the FDA is best expressed in new drug application (NDA) approval packages, and the analysis of relevant data in these documents offers a unique and detailed understanding of the risk of pharmacokinetic DDIs in the clinical context of the various represented therapeutic classes. The aim of the present review was to summarize the most significant clinical DDIs associated with the 2020 NDAs, briefly discuss their most likely mechanism(s), and highlight how to best manage the risk of DDI in the targeted patient populations using labeling recommendations.

Materials and Methods

Pharmacokinetic DDI data for small molecular drugs approved by the FDA in 2020 were analyzed using the University of Washington Drug Interaction Database (http://www.druginteractioninfo.org). This analysis was performed following the methodology previously described (Yu et al., 2019). The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the NDA reviews. Clinical DDI study results were obtained from dedicated clinical trials, pharmacogenetic (PGx) studies, and physiologically based pharmacokinetics (PBPK) modeling and population pharmacokinetic analysis that were used as alternatives to dedicated clinical studies. Using available mean area under the time-plasma concentration curve ratios (AUCRs), all clinical studies with AUCRs ≥1.25 and ≤0.8 (i.e., positive DDI results) were analyzed. Applying the categorization recommended by the FDA, any drug

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ABBREVIATIONS: AUC, area under the time-plasma concentration curve; AUCR, area under the curve ratio; BCRP, breast cancer resistance protein; DDI, drug-drug interaction; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumor; MATE, multiantimicrobial extrusion protein; NDA, new drug application; NME, new molecular entity; NTI, narrow therapeutic index; OATP, organic anion–transporting polypeptide; OCT, organic cation transporter; PBPK, physiologically-based pharmacokinetics; P-gp, P-glycoprotein; PGx, pharmacogenetic(s).

interactions with area under the time-plasma concentration curve (AUC) changes ≥5-fold (i.e., AUCRs ≥5 or ≤0.2), 2- to 5-fold (2 ≤ AUCR < 5 or 0.2 < AUCR ≤ 0.5), or 1.25- to 2-fold (1.25 ≤ AUCR < 2 or 0.5 < AUCR ≤ 0.8) were considered strong, moderate, or weak drug interactions, respectively.

Results

A total of 40 new molecular entities (NMEs) were approved by the FDA in 2020, and their chemical structures are presented as Supplemental Data (Supplemental Table 1). Similar to what was observed with drugs approved from 2013 to 2017 (Yu et al., 2018, 2019), antineoplastic agents were found to be the most represented therapeutic area, comprising 30% of all approved drugs (Fig. 1). Among the 12 oncology drugs, 8 were kinase inhibitors, highlighting the continuous major role of this therapeutic class in cancer therapy. Interestingly, four new drugs were indicated for the treatment of non–small cell lung cancer, namely capmatinib, lurbinectedin, pralsetinib, and selpercatinib, bringing new therapeutic options for the treatment of a disease with often still poor outcome. Anti-infective agents (N = 4, including one antimalarial, two antiparasitics, and two antivirals) were the second represented class; however, their overall proportion was much smaller (12%) compared with previous years (20% and 23% for NDAs approved in 2013–2016 and 2017, respectively). Central nervous system agents comprised 12% of the approved drugs, which is followed by diagnostic agents (10%) and metabolism/gastrointestinal agents (10%). About one-third of the drugs (N = 14; 35%) were considered first-in-class, a strong indicator of the continuous innovation of the pharmaceutical industry, and more than half (N = 22; 55%) of all drugs were approved under the orphan disease approval process.

Metabolism- and Transport-Based DDIs

Except for two diagnostic agents and an osmotic laxative used to treat chronic idiopathic constipation, all NDAs (N = 37) included in vitro and clinical drug metabolism and transport interaction data. Among them, 25 NDAs had clinical drug interaction data available, 4 presented PGx information, 6 had PBPK simulation data, and 3 had population pharmacokinetic analysis. Following the regulatory recommended approach (FDA, 2020r), drug interaction studies using index or clinical substrates, inhibitors, and inducers were systemically performed when in vitro evaluations suggested a possible risk of clinical interactions. There were approximately 180 DDI studies with AUCRs meeting the criteria for positive interaction (AUCRs ≥1.25 or ≤0.8): 82 inhibition DDIs (plus 5 PGx studies) and 31 induction interaction studies in which NMEs were the substrates (or victim drugs) and 55 inhibition interaction studies and 7 induction DDIs in which NMEs were the precipitants (or perpetrators). Almost all clinical DDIs with an AUC change of at least 2-fold triggered label recommendations due to possible safety issues or lack of efficacy, and these interactions are discussed in detail in the following sections. For drug interactions with AUC changes less than 2-fold, most were not considered clinically relevant, and only those leading to specific clinical recommendations are briefly reviewed below.

Other Mechanism of DDIs

In addition to metabolism- and transporter-based DDIs, 12 new drugs were evaluated for gastric pH-dependent DDIs, with 9 using dedicated clinical trials and 3 evaluated with population pharmacokinetic analysis. Ten of them were class II or IV drugs according to the Biopharmaceutics Classification System, with pH-dependent solubility. Ten drugs were indicated for cancer treatment, including seven kinase inhibitors. Proton pump inhibitors (e.g., esomeprazole, omeprazole, pantoprazole, rabeprazole) and histamine receptor-2 antagonists (e.g., famotidine, ranitidine) were the acid-reducing agents used as perpetrators in the clinical studies. The greatest change in exposure was observed for selpercatinib, a kinase inhibitor indicated for the treatment of non–small cell lung cancer and thyroid cancer. Under fasted conditions, omeprazole coadministration decreased selpercatinib AUC and C_{max} by 69% and 88%, respectively, and it is therefore recommended to avoid concomitant use of a proton pump inhibitor, a histamine receptor-2 receptor antagonist, or a locally acting antacid with selpercatinib. If concomitant use cannot be avoided, the risk of DDI can be mitigated by taking food or staggering dosing with acid-reducing agents (FDA, 2020a).

NMEs as Substrates

DDIs with AUC Changes ≥2-Fold. There were approximately 60 moderate-to-strong drug interaction studies involving 15 NMEs as substrates, with more than half (N = 8) being oncology drugs. Inhibition and induction of CYP3A explained most of these interactions (about 90%). All drug interactions with AUC change ≥5-fold are presented in Table 1, with the maximum AUCR observed listed.

Based on the results of mechanistic studies with clinical index inhibitors, three drugs were identified as sensitive substrates, namely avapritinib and lonafarnib for CYP3A and relugolix for P-glycoprotein (P-gp). When concurrently administered with the strong CYP3A inhibitor itraconazole (200 mg once daily for 14 days) in healthy subjects, avapritinib, a kinase inhibitor indicated for the treatment of gastrointestinal stromal tumor (GIST), exhibited a 4.32-fold increase in AUC (after 200-mg single dose). A higher change of 7.00-fold in healthy subjects

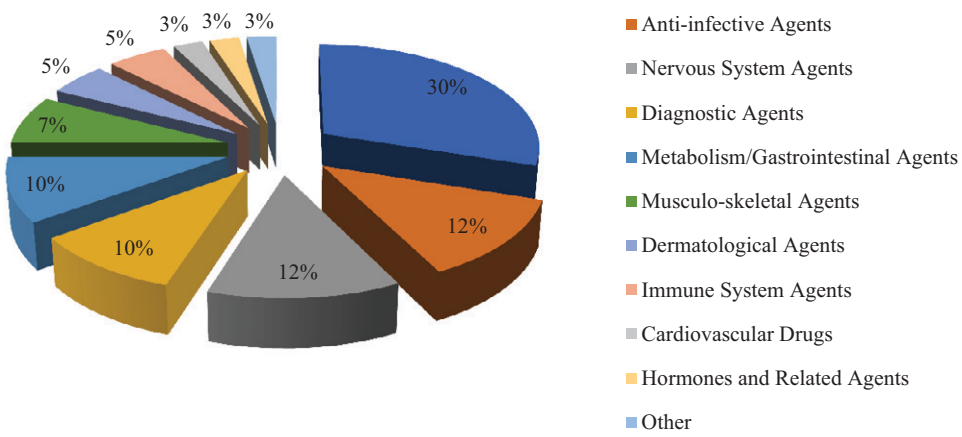

Fig. 1. Therapeutic classes of drugs (small molecules) approved in 2020. Other refers to a new class of drug, indicated to reduce the risk of death due to rare genetic diseases that cause premature aging.

TABLE 1

Drug interactions with AUC changes ≥5 in the victim drugs

Maximum AUCR is presented for the same mechanism; for each section, DDIs are arranged based on the AUCR; all studies were conducted in healthy subjects unless otherwise specified (this information was not available for elugolix in the NDA review or the drug label).

Substrate (Dosage)	Precipitant (Dosage)	NME Therapeutic Class	AUCR	C_{max} Ratio	Enzyme or Transporter Primarily Involved	Label Impact	Reference
Inhibition DDIs with AUCRs ≥5, NMEs as substrates							
Avapritinib (300 mg QD at steady state)	Itraconazole (200 mg QD at steady state)	Antineoplastic Agents	7.00 (PBPK in healthy subjects), 7.90 (PBPK in patients)	6.21 (PBPK in healthy subjects), 6.91 (PBPK in patients)	CYP3A	Avoid strong CYP3A inhibitors	(FDA, 2020b)
Relugolix (20 mg SD)	Erythromycin (NP)	Antineoplastic Agents	6.25	6.18	P-gp[a]	Avoid oral P-gp inhibitors; if unavoidable, separate dose of at least 6 hours	(FDA, 2020i)
Lonafarnib (50 mg SD)	Ketoconazole (200 mg QD for 5 days)	Other[b]	5.07	3.60	CYP3A[c]	contraindicated with strong or moderate CYP3A inhibitors; avoid weak CYP3A inhibitors, if unavoidable, reduce dose of lonafarnib; monitor for adverse reactions, such as arrhythmias, and events, such as syncope and heart palpitations	(FDA, 2020p)
Induction DDIs with AUCRs ≤0.2, NMEs as substrates							
Lonafarnib (50 mg SD with ritonavir 100 mg)	Rifampin (600 mg QD for 8 days)	Other	0.02	0.08	CYP3A[c]	Contraindicated with strong or moderate CYP3A inducers	(FDA, 2020p)
Avapritinib (400 mg SD)	Rifampin (600 mg QD for 18 days)	Antineoplastic Agents	0.08	0.29	CYP3A	Avoid strong CYP3A inducers	(FDA, 2020b)
Selpercatinib (160 mg SD)	Rifampin (600 mg QD for 11 days)	Antineoplastic Agents	0.13	0.30	CYP3A[c]	Avoid strong CYP3A inducers	(FDA, 2020a)
Pemigatinib (13.5 mg SD)	Rifampin (600 mg QD for 9 days)	Antineoplastic Agents	0.15	0.38	CYP3A[c]	Avoid strong CYP3A inducers	(FDA, 2020j)
Fostemsavir (1200 mg SD)	Rifampin (600 mg QD for 7 days)	Anti-infective Agents	0.18 (temsavir)	0.24 (temsavir)	CYP3A[c]	Contraindicated with strong CYP3A inducers	(FDA, 2020k)
Rimegepant (75 mg SD)	Rifampin (600 mg QD for 11 days)	Migraine Treatments	0.20	0.38	CYP3A4[c]	Avoid strong or moderate CYP3A4 inducers	(FDA, 2020g)
Inhibition DDIs with AUCRs ≥5, NMEs as precipitants							
Decitabine (20 mg SD)	Cedazuridine (100 mg QD for 4 days)	Antineoplastic Agents	12.00[d]	NP	Cytidine deaminase	Avoid coadministration of cedazuridine and decitabine with drugs that are metabolized by cytidine deaminase	(FDA, 2020d)
Midazolam (3 mg SD)	Lonafarnib (100 mg BID for 5 days)	Other	7.39	2.80	CYP3A	contraindicated with midazolam and the HMG CoA reductase inhibitors lovastatin, simvastatin, and atorvastatin; avoid other sensitive CYP3A substrates, if unavoidable, monitor for adverse reactions and reduce the dose of those sensitive CYP3A substrates according to their product labeling; for certain CYP3A substrates where minimal concentration changes may lead to serious or life-threatening toxicities, monitor for adverse reactions and reduce	(FDA, 2020p)

TABLE 1 *continued*

Substrate (Dosage)	Precipitant (Dosage)	NME Therapeutic Class	AUCR	C_{max} Ratio	Enzyme or Transporter Primarily Involved	Label Impact	Reference
Midazolam (2 mg SD)	tucatinib (300 mg BID for 10 days)	Antineoplastic Agents	5.74	3.01	CYP3A	the dose of the CYP3A substrate in accordance with the product labeling avoid CYP3A substrates wherein minimal concentration changes may lead to serious or life-threatening toxicities; if unavoidable, reduce dose of the CYP3A substrate in accordance with its approved product labeling	(FDA, 2020n)

BID, twice daily; MD, multiple doses; NP, not provided; QD, once daily; SD, single dose.
[a]Inhibiton of CYP3A may be also involved. However, compared with the DDI study result with CYP3A inhibitors, the increase in relugolix exposure is likely primarily driven by the increase in oral bioavailability due to inhibition of intestinal P-gp efflux by erythromycin. A postmarketing commitment was issued to conduct a pharmacokinetic study to evaluate the effect of P-gp inhibitors administered after relugolix to further inform dosing strategy.
[b]Other refers to a new class of drug, indicated to reduce the risk of death due to rare genetic diseases that cause premature aging.
[c]In vitro, the NME was a substrate of P-gp. Inhibiton or induction of P-gp may also contribute to the NME exposure change.
[d]The study was conducted in patients with myelodysplastic syndromes or chronic myelomonocytic leukemia.

and 7.90-fold in patients with GIST in avapritinib steady-state AUC (after the clinical dose of 300 mg once daily) was predicted using PBPK modeling and simulations. The effect of moderate and weak CYP3A inhibitors was also predicted using the same approach. Erythromycin (500 mg three times daily), fluconazole (200 mg once daily), and verapamil (80 mg three times daily), all moderate CYP3A inhibitors, were predicted to increase avapritinib steady-state AUC 2- to 3-fold in patients with GIST, whereas the weak CYP3A inhibitor cimetidine (400 mg three times daily) was not predicted to affect avapritinib exposure (FDA, 2020b). Because higher plasma concentrations of avapritinib may increase the incidence and severity of adverse reactions, concomitant administration with strong and moderate CYP3A inhibitors should be avoided. If coadministration with a moderate CYP3A inhibitor cannot be avoided, the dose of avapritinib should be reduced (FDA, 2020b). Lonafarnib is an orphan drug used to reduce the risk of death due to Hutchinson-Gilford progeria syndrome and for the treatment of certain processing-deficient progeroid laminopathies in patients 12 months of age and older. Coadministration with ketoconazole (200 mg once daily for 5 days), a strong CYP3A inhibitor, resulted in a 5.07-fold increase in lonafarnib AUC in healthy subjects (FDA, 2020p). CYP3A inhibitors with lower potency were not evaluated but were expected to increase lonafarnib exposure to a clinically meaningful extent. Therefore, because of safety concerns, the use of lonafarnib with strong or moderate CYP3A inhibitors is contraindicated. Concomitant use of lonafarnib with weak CYP3A inhibitors should be avoided as well; however, if coadministration is unavoidable, the dose of lonafarnib should be reduced. Additionally, patients should be monitored for adverse reactions, such as arrhythmias and other cardiovascular events like syncope and heart palpitations, as the effect of lonafarnib on QT interval is unknown (FDA, 2020p). Finally, exposure to the oncology drug relugolix was found to increase when coadministered with erythromycin (6.25-fold increase in AUC and 6.18-fold increase in C_{max}), primarily due to inhibition of intestinal P-gp. In vitro, relugolix was a P-gp substrate, with an efflux ratio of 16.4 in Caco-2 cells. Although contribution of CYP3A cannot be fully ruled out because relugolix was metabolized by CYP3A in vitro and erythromycin is also a moderate CYP3A inhibitor, CYP3A is expected to play a minimal role given that a much smaller increase (1.21- to 1.51-fold) in the exposure of relugolix was observed in the presence of moderate and strong CYP3A inhibitors (FDA, 2020i).

Compared with the inhibition results, more drugs ($N = 6$) were sensitive to induction. In addition to avapritinib and lonafarnib, fostemsavir (prodrug, active moiety temsavir), rimegepant, pemigatinib, and selpercatinib were all sensitive to CYP3A induction, with AUC decreases of 81%–87% after concomitant administration of multiple doses of rifampin, an index inducer of CYP3A. Notably, induction of P-gp may also be involved in these interactions, as all were P-gp substrates in vitro except avapritinib (FDA, 2020a,b,g,j,k,p). To avoid reduced efficacy associated with the significant decrease in drug exposure, concomitant use with strong CYP3A inducers is either contraindicated or should be avoided for these drugs (FDA, 2020a,b,g,j,k,p).

Regarding moderate inhibition, 10 drugs were found to be moderate sensitive substrates (AUCRs 2–5) based on inhibition or PGx results: fostemsavir (CYP3A), oliceridine (CYP2D6), ozanitib [breast cancer resistance protein (BCRP)], pemigatinib (CYP3A), pralsetinib (CYP3A), rimegepant (CYP3A), selpercatinib (CYP3A), tazemetostat (CYP3A), tucatinib (CYP2C8), and vibegron (P-gp). Oliceridine, an opioid agonist indicated for the management of severe acute pain, was primarily metabolized by CYP2D6 and CYP3A4 in vitro. The moderate sensitivity to CYP2D6 inhibition was identified through PGx studies, wherein CYP2D6 poor metabolizers showed approximately 2-fold higher exposure to oliceridine compared with normal metabolizers. The effect of concomitant administration of a CYP2D6 inhibitor on oliceridine

pharmacokinetics has not been evaluated but is expected to be similar to what was observed in CYP2D6 poor metabolizers based on population pharmacokinetic analyses. An approximate 4-fold increase in oliceridine AUC and 70% reduction in clearance were expected in CYP2D6 normal metabolizers in the worst-case scenario of concomitant inhibition of both CYP3A4 and CYP2D6 enzymes, whereas coadministration with itraconazole, a strong CYP3A inhibitor, was estimated to reduce oliceridine clearance by 45% (FDA, 2020h). On the other hand, based on induction studies, three kinase inhibitors (capmatinib, pralsetinib, and selumetinib) were found to be moderate sensitive substrates of CYP3A, with coadministration of multiple doses of rifampin significantly reducing their exposure by 51%–68% (FDA, 2020c,f,l). Most of DDIs mentioned above led to specific label recommendations when concomitantly administered with known inhibitors or inducers. For instance, it is recommended to avoid concomitant use of selpercatinib with strong CYP3A inhibitors; if coadministration is unavoidable, the dose of selpercatinib should be reduced by half. In addition, because selpercatinib can cause QT prolongation, it is suggested to monitor the QT interval with ECGs more frequently (FDA, 2020a,o). For ozanimod, a drug indicated for the treatment of multiple sclerosis, coadministration with inhibitors of BCRP is not recommended (FDA, 2020o).

DDIs with AUC Changes <2-Fold but with Clinical Implications. There were about 50 studies with AUCR 1.25–2 or 0.5–0.8 involving NMEs as substrates, but less than half led to clinical recommendations. Inhibition or induction of CYP3A explained more than 60% of these results, and the majority of studies were evaluations of sensitive substrates with less potent inhibitors or inducers. Additionally, the following seven drugs were found to be weak substrates based on studies with strong inhibitors (itraconazole for CYP3A, gemfibrozil for CYP2C8, and cyclosporine for P-gp and BCRP): berotralstat (P-gp, BCRP), capmatinib (CYP3A), oliceridine (CYP3A), ozanimod (CYP2C8), relugolix (CYP3A), rimegepant (CYP2C9; PGx study), and ripretinib (CYP3A). Given the smaller change in the drugs' exposure, label recommendations are mostly to monitor for adverse events and reduce dose or dosing frequency as needed. However, a few drugs have stricter recommendations because of a narrower therapeutic range. For instance, it is recommended to avoid coadministration of strong or moderate CYP3A4 inhibitors or fluconazole with selumetinib, a kinase inhibitor to treat neurofibromatosis type 1. If coadministration cannot be avoided, the dose of selumetinib should be reduced (FDA, 2020f). Similarly, for ozanimod, "Coadministration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended" (FDA, 2020o).

NMEs as Precipitants

DDIs with AUC Changes ≥2-Fold. There were only 10 moderate-to-strong drug interactions involving NMEs as precipitants, and all were related to inhibition, with no strong or moderate inducer of enzymes or transporters identified. Inhibition of CYP3A explained about half of the interactions. A total of seven drugs were involved, with more than half ($N = 4$) indicated for cancer treatment. All interaction results led to label recommendations to mitigate the risk of DDI in clinical settings.

Three drugs were considered strong inhibitors of enzymes (victim drug AUCR ≥5): cedazuridine for cytidine deaminase, lonafarnib for CYP3A, and tucatinib for CYP3A (Table 1). No drug exhibited strong inhibition of transporters. Notably, cedazuridine, indicated in combination with decitabine for the treatment of myelodysplastic syndromes, is used to prevent the rapid metabolism of decitabine in the gastrointestinal tract to allow for oral administration and therefore increase systemic exposure of decitabine. Following different dosing regimen, cedazuridine was found to increase the AUC of decitabine up to 12-fold (FDA, 2020d). Because cedazuridine is a strong inhibitor of cytidine deaminase, coadministration of the combination drug with drugs metabolized by cytidine deaminase may result in increased exposure with potential for increased toxicity of these drugs. Therefore, coadministration of cedazuridine and decitabine with drugs that are metabolized by cytidine deaminase should be avoided (FDA, 2020d). Regarding lonafarnib and tucatinib, both caused a significant increase in the AUC of midazolam, an index substrate of CYP3A (7.39- and 5.74-fold, respectively). The clinical trials were performed because in vitro results suggested that both drugs have the potential to inhibit CYP3A at clinically relevant concentrations. In vitro, both were mechanism-based inhibitors of CYP3A ($K_I = 0.54$ μM and $k_{inact} = 0.011$/min for tucatinib; values not provided for lonafarnib in the NDA review), and tucatinib was found to also reversibly inhibit CYP3A with a K_i value of 0.805 μM (FDA, 2020n,p).

Additionally, the following four drugs were found to be moderate inhibitors: berotralstat (CYP2D6 and CYP3A), capmatinib (CYP1A2 and BCRP), osilodrostat (CYP1A2 and CYP2C19), and selpercatinib (CYP2C8), with increases in the index substrates of 2- to 3-fold. Label recommendations are provided regarding concomitant medications that are substrates of these cytochrome P450 isoforms or BCRP transporter with a narrow therapeutic index (NTI). For example, both osilodrostat (indicated for the treatment of Cushing's disease) and capmatinib (a kinase inhibitor to treat metastatic non–small cell lung cancer) increased the AUC of the CYP1A2 index substrate caffeine to a similar extent (AUCRs of 2.50 and 2.43, respectively), with no change in its C_{max}. Both labels give recommendations regarding concomitant administration of CYP1A2 substrates with an NTI. For osilodrostat, it is recommended to use with caution or decrease dose of the substrate drug when coadministered with CYP1A2 substrates with an NTI (FDA, 2020e). If concomitant use is unavoidable between capmatinib and CYP1A2 substrates, in which minimal concentration changes may lead to serious adverse reactions, dose of the CYP1A2 substrates should be decreased in accordance with its approved prescription information (FDA, 2020l).

DDIs with AUC Changes <2-fold but with Clinical Implications. There were 56 studies showing weak inhibition or induction. Similarly to the substrate studies, only 40% of these interactions were considered clinically relevant. Eight drugs weakly inhibited one or two specific cytochrome P450 enzymes, leading to label recommendations for only two of them, namely lonafarnib (CYP2C19) and selpercatinib (CYP3A). Regarding induction studies, three drugs exhibited weak induction, but only one drug, tazemetostat, had label recommendations based on the results. Indeed, tazemetostat, an orphan drug for epithelioid sarcoma, was found to decrease the AUC of midazolam by 37% when coadministered in patients with cancer at the dose of 800 mg twice daily, due to induction of CYP3A. It is noted in the label that "coadministration of CYP3A substrates, including hormonal contraceptives, with tazemetostat can result in decreased concentrations and reduced efficacy of CYP3A substrates" (FDA, 2020m).

About a third of these weak interactions were mediated by drug transporters, involving P-gp, BCRP, organic anion–transporting polypeptide (OATP) 1B1/1B3, organic cation transporter (OCT) 2, and multiantimicrobial extrusion protein (MATE) 1/2-K. Regarding inhibition of renal transporters, in vitro capmatinib inhibited MATE1 ($K_i = 0.28$ μM) and MATE2-K ($K_i = 0.29$ μM), pemigatinib inhibited MATE1 ($IC_{50} = 0.075$ μM) and OCT2 ($IC_{50} = 1.1$ μM), selpercatinib inhibited MATE1 ($IC_{50} = 0.666$ μM), and tucatinib inhibited MATE1 ($IC_{50} = 0.0855$ μM) and MATE2-K ($IC_{50} = 0.135$ μM) as well as OCT2 ($IC_{50} = 0.107$ μM). Because of the potential inhibition of MATEs and OCT2 in vivo by these four oncology drugs, endogenous creatinine was measured as the marker of renal function as well as activity of MATEs and OCT2. For capmatinib, all subjects showed transient grade 1 serum creatinine increase postdose during a 72-hour sampling period. According to the NDA review, these results indirectly suggest that reversible

inhibition of renal transporters (i.e., MATE1 and MATE2-K) may explain the increase in serum creatinine. Based on this observation, the label states that "coadministration of capmatinib may increase the exposure of MATE1 and MATE2-K substrates, which may increase the adverse reactions of these substrates. If coadministration is unavoidable between capmatinib and MATE1 or MATE2-K substrates where minimal concentration changes may lead to serious adverse reactions, dose of MATE1 or MATE2K substrate should be decreased in accordance with the approved prescribing information" (FDA, 2020l). For pemigatinib, endogenous serum creatinine was found to increase an average of 0.2 mg/dl within the first 21-day cycle of treatment, whereas for selpercatinib and tucatinib, a mean increase of 1.18- to 1.32-fold in endogenous serum creatinine was observed in clinical studies, and their labels suggest that "alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed" (FDA, 2020a,j,n).

Discussion

The systematic mechanistic framework of pharmacokinetic drug interactions evaluation during drug development continues to provide essential information for the management of DDIs in the clinic since the use of index substrates, inhibitors, and inducers of enzymes and transporters enables extrapolations with multiple comedications and guides the safe and effective use of new drug products. In the present analysis, pharmacokinetic-based DDI data from NDA reviews for drugs approved by the FDA in 2020 were thoroughly reviewed, and the clinical significance of the interactions was assessed based on label recommendations. As expected from previous similar evaluations (Yu et al., 2014, 2018, 2019), CYP3A mediated the majority of interactions, with NMEs either substrates or precipitants. Indeed, of the 10 largest interactions with AUC changes of the victim drug equal to or greater than 5-fold, eight were mediated by CYP3A (Table 1). Most of the clinical evaluations were performed using index drugs recommended by the FDA DDI guidance. Endogenous biomarkers were also used with seven drugs: 4-β-hydroxycholesterol for tazemetostat and creatinine for bempedoic acid, capmatinib, pemigatinib, rimegepant, selpercatinib, and tucatinib, highlighting the growing interest of using these biomarkers for the clinical evaluation of DDIs. The CYP3A4 endogenous marker 4-β-hydroxycholesterol was measured in patients with cancer after tazemetostat treatment. There was a 1.70-fold increase in the exposure of this marker, consistent with the midazolam study results (a 37% decrease in AUC), further confirming induction of CYP3A by tazemetostat. Endogenous creatinine was measured to assess the activity of the renal transporters MATE1/2-K and OCT2, and the observed changes in serum creatinine levels were used to guide label recommendations for four drugs (FDA, 2020a,j,l,n). This seems to be a relatively new approach, as this was not observed in previous years, in which drugs with potential to inhibit renal transporters were evaluated with substrates like metformin or cephalexin (Yu and Ragueneau-Majlessi, 2020). Similar to drugs approved between 2013 and 2019 though (Yu et al., 2014, 2018; Yu and Ragueneau-Majlessi, 2020), no drugs approved in 2020 exhibited greater than 2-fold change in exposure of the substrate drug transported by MATEs and OCT2, suggesting overall a relatively limited risk of overexposure when inhibiting these renal transporters. Endogenous biomarkers, such as coproporphyrins, have been proposed for assessing OATP1B1/1B3-mediated DDIs (Lai et al., 2016; Chu et al., 2017). However, none of these biomarkers were measured with the 2020 drugs. For example, bempedoic acid and fostemasavir inhibited OATP1B1/1B3 in vitro, and clinical studies with different statins were conducted to investigate the clinical relevance of this inhibition (FDA, 2020k,q).

Regarding labeling recommendations based on DDI study results, almost all drug interactions with AUC changes of at least 2-fold led to specific label recommendations, with all larger DDIs (AUC change $\geq$5-fold) leading to either contraindication or avoidance of concomitant administration. For DDIs with AUC changes less than 2-fold, labeling recommendations were primarily related to NTI drugs. Finally, it is worth noting the substantial contribution of oncology drugs to the largest clinical interactions involving NMEs identified as sensitive substrates and strong inhibitors. This highlights the significant risk of pharmacokinetic DDIs and the need for clear and assertive mitigation strategies in patients with cancer for whom therapeutic management is complex due to polytherapy and the coadministration of interacting drugs is often difficult to avoid.

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Authorship Contributions

Participated in research design: Yu, Ragueneau-Majlessi.

Performed data analysis: Yu, Wang, Ragueneau-Majlessi.

Wrote or contributed to the writing of the manuscript: Yu, Wang, Ragueneau-Majlessi.

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Food and Drug Administration (FDA) (2020b) *Drug Approval Package: AYVAKIT (avapritinib). FDA Application NDA 212608*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020c) *Drug Approval Package: GAVRETO (pralsetinib). FDA Application NDA 213721*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020d) *Drug Approval Package: INQOVI (cedazuridine; decitabine). FDA Application NDA 212576*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020e) *Drug Approval Package: ISTURISA (osilodrostat). FDA Application NDA 212801*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020f) *Drug Approval Package: KOSELUGO (selumetinib). FDA Application NDA 213756*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020g) *Drug Approval Package: NURTEC ODT (rimegepant). FDA Application NDA 212728*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020h) *Drug Approval Package: OLINVYK (oliceridine). FDA Application NDA 210730*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020i) *Drug Approval Package: ORGOVYX (relugolix). FDA Application NDA 214621*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020j) *Drug Approval Package: PEMAZYRE (pemigatinib). FDA Application NDA 213736*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020k) *Drug Approval Package: RUKOBIA (fostemsavir). FDA Application NDA 212950*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020l) *Drug Approval Package: TABRECTA (capmatinib). FDA Application NDA 213591*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020m) *Drug Approval Package: TAZVERIK (tazemetostat). FDA Application NDA 211723*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020n) *Drug Approval Package: TUKYSA (tucatinib). FDA Application NDA 213411*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020o) *Drug Approval Package: ZEPOSIA (ozanimod). FDA Application NDA 209899*, FDA, Silver Spring, MD.

Food and Drug Administration (FDA) (2020p) *Drug Approval Package: ZOKINVY (lonafarnib). FDA Application NDA 213969*, FDA, Silver Spring, MD.

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Title: Pharmacokinetic Drug-Drug Interactions with Drugs Approved by the U.S. Food and Drug Administration in 2020: Mechanistic Understanding and Clinical Recommendations

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Journal: Drug Metabolism and Disposition

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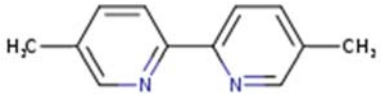
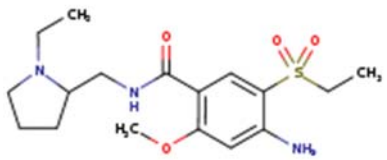
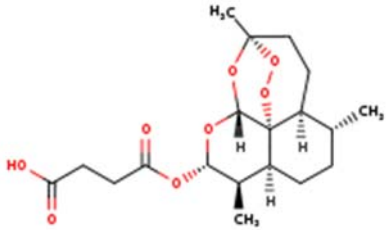
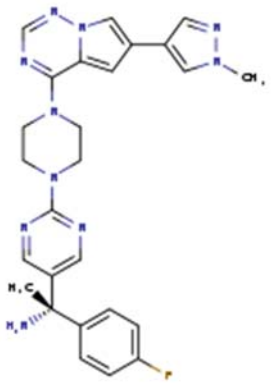
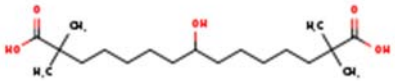
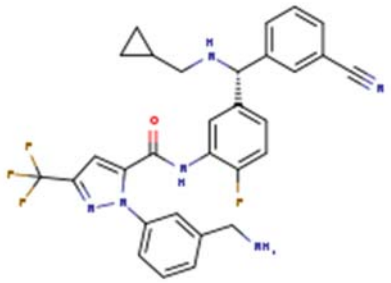
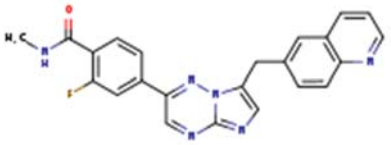
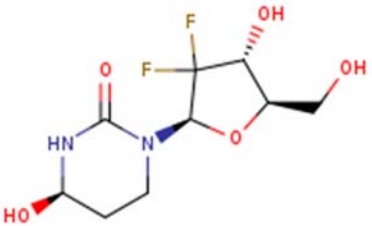
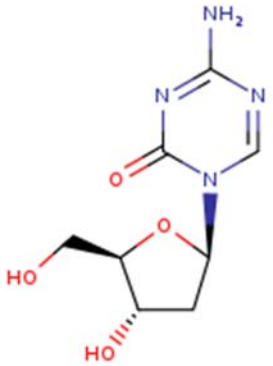
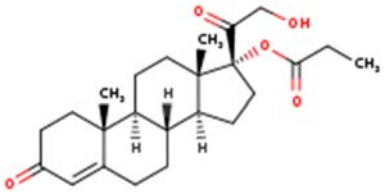
Supplemental Table 1. Clinical indications and chemical structures of small molecular drugs approved by the FDA in 2020

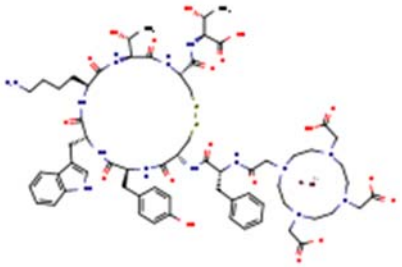
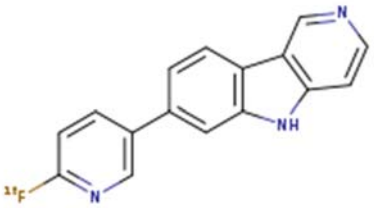
NDA Number	**Drug Name (CAS Registry Number)**	**Clinical Indications[a]**	**Structure[b]**
206966	abametapir (1762-34-1)	a pediculicide indicated for the topical treatment of head liceinfestation in patients 6 months of age and older	

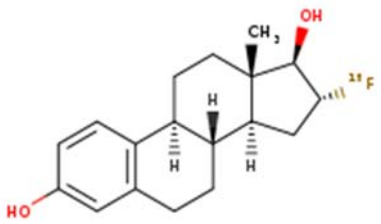
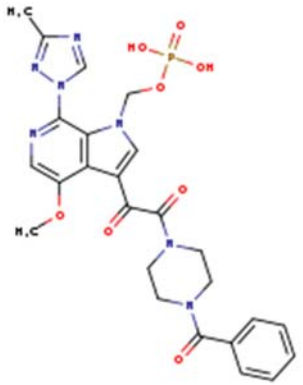
209510	amisulpride (71675-85-9)	a dopamine-2 antagonist indicated in adults for: (1) prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class; (2) treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis	
213036	artesunate (88495-63-0)	an antimalarial indicated for the initial treatment of severe malaria in adult and pediatric patients	

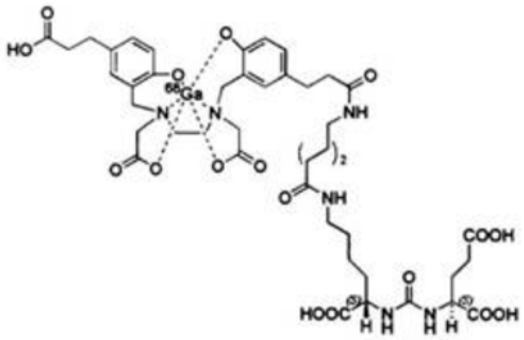
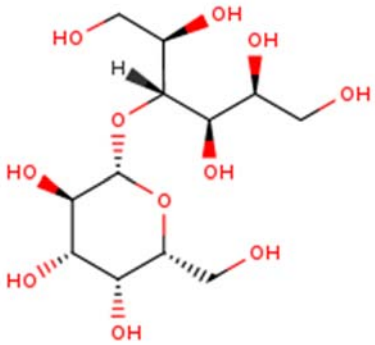
212608	avapritinib (1703793-34-3)	a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor harboring a platelet-derived growth factor receptor alpha exon 18 mutation	
211616	bempedoic acid (738606-46-7)	an adenosine triphosphate-citrate lyase inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C	

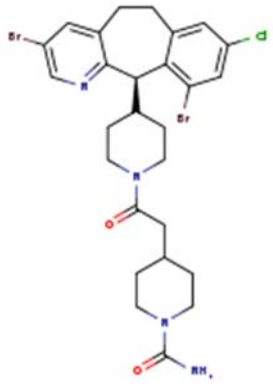
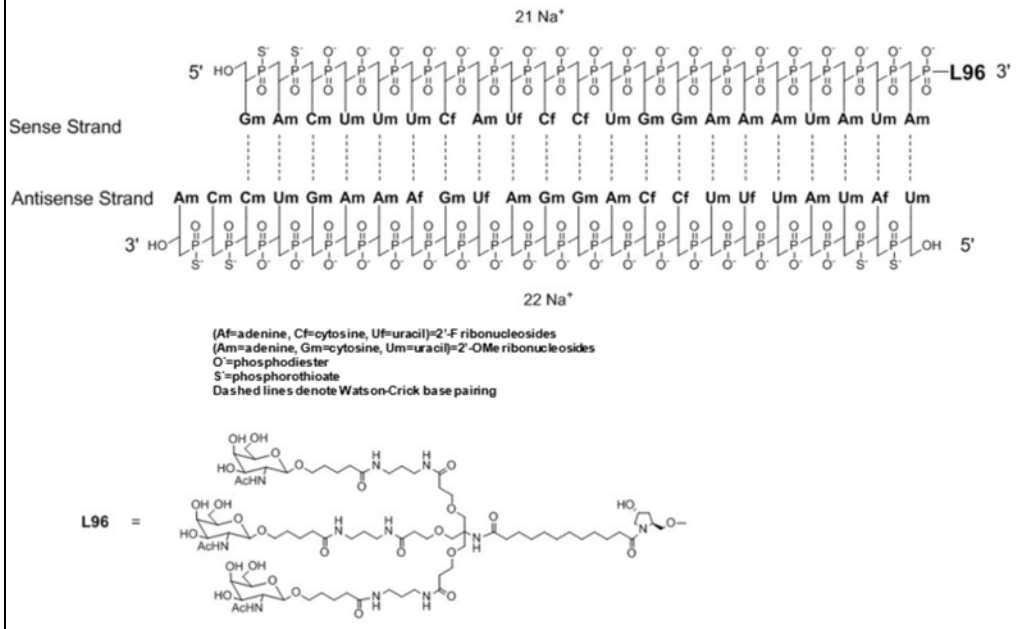
214094	berotralstat (1809010-50-1)	a kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema in adults and pediatric patients 12 years and older	
213591	capmatinib (1029712-80-8)	a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer whose tumors have a mutation that leads to mesenchymal-epithelial transition exon 14 skipping	

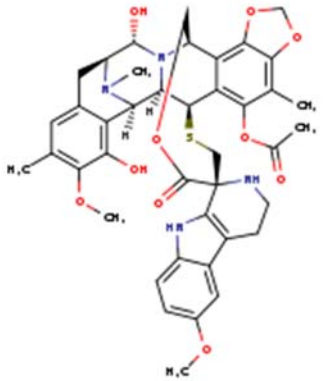
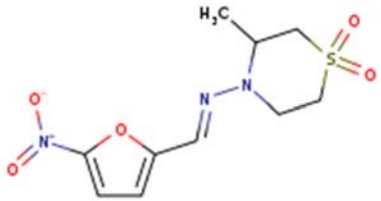
212576	cedazuridine and decitabine (1141397-80-9 and 2353-33-5)	cedazuridine, a cytidine deaminase inhibitor, co-packaged with decitabine, a nucleoside metabolic inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes	 
213433	clascoterone (19608-29-8)	an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients 12 years of age or older	

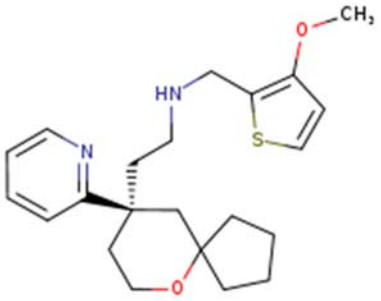
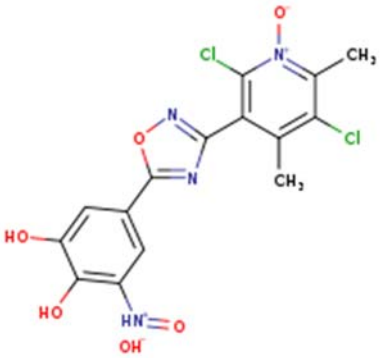
213227	copper Cu-64 dotatate (1426155-87-4)	a radioactive diagnostic agent indicated for use with positron emission tomography for localization of somatostatin receptor positive neuroendocrine tumors in patients	
212123	flortaucipir F 18 (1522051-90-6)	a radioactive diagnostic agent containing the isotope fluorine 18. It is indicated for the evaluation of suspected Alzheimer's disease via positron emission tomography imaging of the brain	

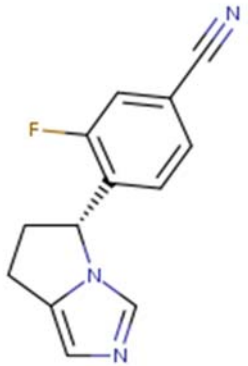
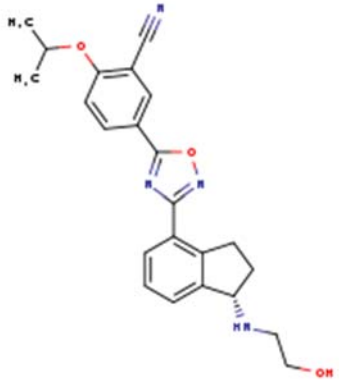
212155	fluoroestradiol F-18 (94153-53-4)	a radioactive diagnostic agent indicated for use with positron emission tomography imaging for the detection of estrogen receptor-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer	
212950	fostemsavir (864953-29-7)	a human immunodeficiency virus type 1 (HIV-1) gp120-directed attachment inhibitor, in combination with other antiretroviral(s), indicated for the treatment of HIV-1 infection in heavily treatment-experienced patients with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations	

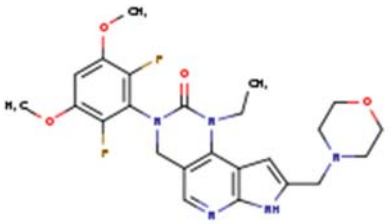
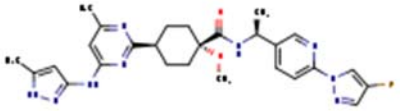
212642	gallium GA 68 PSMA-11 (1906894-20-9)	a peptide-based radioactive diagnostic agent indicated for positron emission tomography imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer meeting certain criteria	
211281	lactitol (585-86-4)	an osmotic laxative indicated for the treatment of chronic idiopathic constipation in adults	

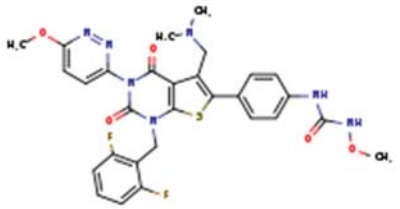
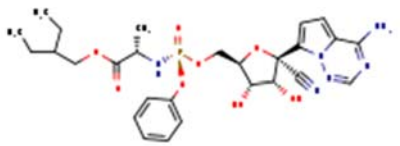
213969	lonafarnib (193275-84-2)	a farnesyltransferase inhibitor indicated in patients 12 months and older for the treatment of Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies	
214103	lumasiran (1834610-13-7)	a hydroxyacid oxidase 1-directed small interfering ribonucleic acid indicated for the treatment of primary hyperoxaluria type 1 in pediatric and adults	

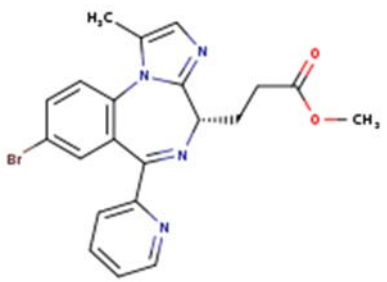
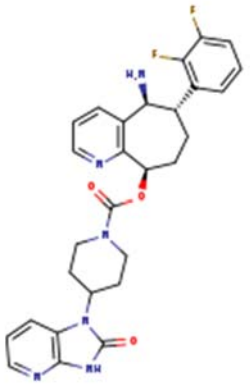
213702	lurbinectedin (497871-47-3)	an alkylating drug indicated for the treatment of adult patients with metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapy	
213464	nifurtimox (23256-30-6)	a nitrofuran antiprotozoal indicated in pediatric patients (birth to less than 18 years of age) for the treatment of Chagas disease (American Trypanosomiasis) caused by Trypanosoma cruzi	

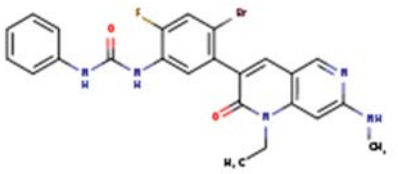
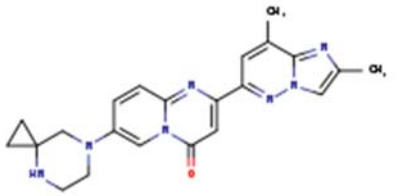
210730	oliceridine (1401028-24-7)	an opioid agonist indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate	
212489	opicapone (923287-50-7)	a catechol-O-methyltransferase inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes	

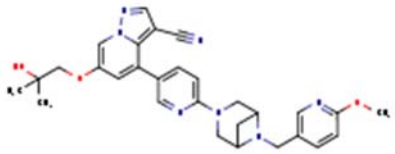
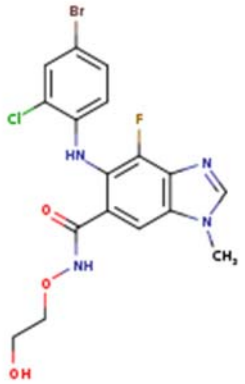
212801	osilodrostat (928134-65-0)	a cortisol synthesis inhibitor indicated for Cushing's disease for whom pituitary surgery is not an option or has not been curative	
209899	ozanimod (1306760-87-1)	a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis	

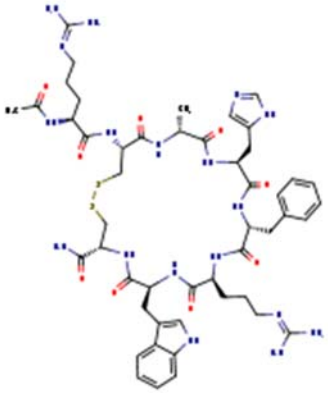
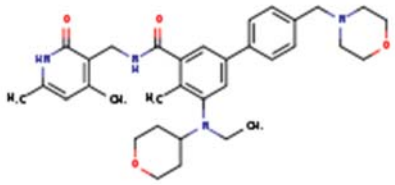
213736	pemigatinib (1513857-77-6)	a kinase inhibitor indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 fusion or other rearrangement	
213721	pralsetinib (2097132-94-8)	a kinase inhibitor indicated for the treatment of metastatic non-small cell lung cancer harboring the rearranged during transfection fusion-positive gene	

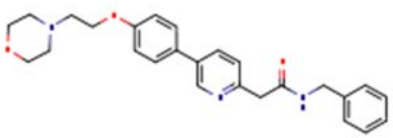
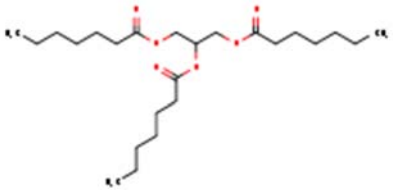
214621	relugolix (737789-87-6)	a gonadotropin-releasing hormone antagonist indicated for the treatment of patients with advanced prostate cancer	
214787	remdesivir (1809249-37-3)	a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for adults and pediatrics (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 requiring hospitalization	

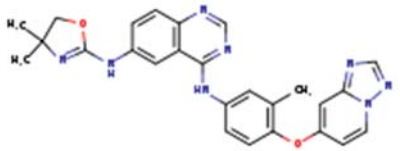
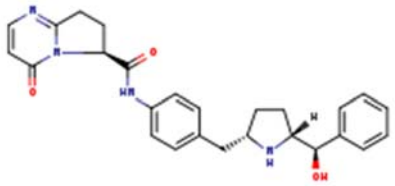
212295	remimazolam (308242-62-8)	a benzodiazepine indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 min or less. It is recommended to individualize and titrate dosing to desired clinical effect	
212728	rimegepant (1289023-67-1)	a calcitonin gene-related peptide receptor antagonist indicated for the treatment of acute migraine in adults	

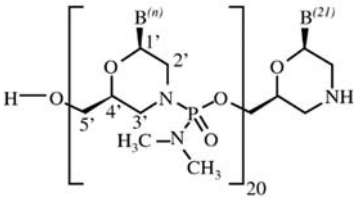
213973	ripretinib (1442472-39-0)	a kinase inhibitor indicated for the treatment of advanced gastrointestinal stromal tumor in patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib	
213535	risdiplam (1825352-65-5)	a survival of motor neuron 2 splicing modifier indicated for the treatment of spinal muscular atrophy	

213246	selpercatinib (2152628-33-4)	a kinase inhibitor indicated for the treatment of non-small cell lung cancer and thyroid cancer with specific RET gene mutations	
213756	selumetinib (606143-52-6)	a kinase inhibitor indicated for the treatment of pediatric patients (2 years and older) with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas	

213793	setmelanotide (920014-72-8)	a melanocortin 4 receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance	
211723	tazemetostat (1403254-99-8)	a methyltransferase inhibitor indicated for the treatment of patients 16 years and older with metastatic or locally advance epithelioid sarcoma not eligible for complete resection	

213189	tirbanibulin (897016-82-9)	a microtubule inhibitor indicated for the topical treatment of actinic keratosis of the face or scalp	
213687	triheptanoin (620-67-7)	a medium-chain triglyceride indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with long-chain fatty acid oxidation disorders	

213411	tucatinib (937263-43-9)	a kinase inhibitor indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer	
213006	vibegron (1190389-15-1)	a beta-3 adrenergic agonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults	

212154	viltolarsen (2055732-84-6)	an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping	 CCTCCGGTTC TGAAGGTGTTC

[a] Clinical indications were obtained from each drug's Product Label available at Drugs@FDA, accessed in September 2021.

[b] Chemical structure was obtained from https://chem.nlm.nih.gov/chemidplus/ accessed August 2021, except gallium GA 68 PSMA-11, lumasiran, and viltolarsen whose structures were obtained from the Gallium GA 68 PSMA-11, OXLUMO, and VILTEPSO Product Label, respectively.