

Regulatory Note

Theme: Towards Integrated ADME Prediction: Past, Present, and Future Directions
Guest Editors: Lawrence X. Yu, Steven C. Sutton, and Michael B. Bolger

Predicting Drug–Drug Interactions: An FDA Perspective

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Abstract. Pharmacokinetic drug interactions can lead to serious adverse events, and the evaluation of a new molecular entity's drug–drug interaction potential is an integral part of drug development and regulatory review prior to its market approval. Alteration of enzyme and/or transporter activities involved in the absorption, distribution, metabolism, or excretion of a new molecular entity by other concomitant drugs may lead to a change in exposure leading to altered response (safety or efficacy). Over the years, various *in vitro* methodologies have been developed to predict drug interaction potential *in vivo*. *In vitro* study has become a critical first step in the assessment of drug interactions. Well-executed *in vitro* studies can be used as a screening tool for the need for further *in vivo* assessment and can provide the basis for the design of subsequent *in vivo* drug interaction studies. Besides *in vitro* experiments, *in silico* modeling and simulation may also assist in the prediction of drug interactions. The recent FDA draft drug interaction guidance highlighted the *in vitro* models and criteria that may be used to guide further *in vivo* drug interaction studies and to construct informative labeling. This report summarizes critical elements in the *in vitro* evaluation of drug interaction potential during drug development and uses a case study to highlight the impact of *in vitro* information on drug labeling.

KEY WORDS: drug development; drug–drug interaction; new drug application; prediction; regulatory and guidance.

INTRODUCTION

The desirable and undesirable effects of a drug are generally related to its concentration at the sites of action, which in turn is related to the amount administered (dose) and to the drug's absorption, distribution, metabolism, and/or excretion (ADME). All these processes can be influenced by both intrinsic and extrinsic factors such as age, race, gender, disease states, concomitantly administered drugs, food, and juices (1). Observed changes arising from pharmacokinetic drug–drug interactions can be substantial such as an order of magnitude or more increase or decrease in the blood and tissue concentrations of a drug or its metabolites. Many of

these interactions involved inhibition of metabolizing enzymes and transporters, resulting in increased systemic exposure and subsequent adverse drug reactions. In other cases, induction of metabolizing enzymes and transporters resulted in reduced systemic exposure leading to a risk of loss of efficacy of co-administered drugs. Therefore, drug interaction potential is recognized as an important consideration in the evaluation of a new molecular entity (NME) (2,3) and is an integral part of drug development and regulatory review prior to NME's market approval.

Several FDA guidance documents developed since the mid-1990s and the most recent draft drug interaction guidance released in September 2006 reflect the Agency's view that the metabolism of an NME and its potential on inhibition and induction of key metabolizing enzymes and transporters should be defined (4–6). Potential drug–drug interactions resulting from the effects of other drugs on NME and the effects of NME on other drugs should be explored during drug development to ensure an adequate assessment of an NME's safety and effectiveness (6,7). An integrated approach (*in vitro* and *in vivo*) to the evaluation of an NME's drug interaction potential may reduce the number of unnecessary studies and optimize knowledge. The recent FDA draft drug interaction guidance highlighted the *in vitro* models and criteria that may be used to guide further *in vivo* drug interaction studies (6). Besides *in vitro* experiments, *in silico* modeling and simulation may also assist in the prediction for drug interactions.

The opinions contained in this paper do not necessarily reflect the official views of the FDA.

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ABBREVIATIONS: ADME, Absorption, distribution, metabolism or excretion; AhR, Aryl hydrocarbon receptor; BCRP, Breast cancer resistance protein; CAR, Constitutive androstane receptor; IND, Investigational new drug; NDA, New drug application; NME, New molecular entity; OAT, Organic anion transporter; OATP, Organic anion transporting polypeptide; OCT, Organic cation transporter; P-gp, P-glycoprotein; UGT, UDP-glucuronosyltransferase.

CURRENT STATUS AND RECOMMENDATION IN PREDICTING *IN VIVO* DRUG INTERACTIONS BASED ON *IN VITRO* EVALUATION

Pharmacokinetic drug interactions can occur via inhibition or induction of metabolic enzymes or transporters. Evaluation of an NME's drug–drug interaction potential is an integrated part of drug development and regulatory review prior to its market approval. In general, three basic questions need to be addressed in the new drug application: (1) Will other drugs alter the exposure to an NME? (2) Will an NME alter the exposure to other drugs? (3) Are these alterations in exposure clinically relevant to warrant dose adjustment? While drug interactions can be evaluated via specific clinical studies in healthy subjects or patients, *in vitro* approaches are now becoming common as a critical first step in the assessment of drug interaction potential via specific pathways, and knowledge obtained from these studies may help reduce the number of unnecessary studies. The experiments are generally conducted during early phase of drug development process. Results from the *in vitro* studies can be used to predict *in vivo* interaction and guide the need for further *in vivo* study evaluation. The 2006 FDA draft drug interaction guidance has specific recommendation as to how to use *in vitro* models to address drug interaction potential and, for the first time, includes criteria for evaluating transporter-based drug interactions (6).

Prediction of Metabolism-Mediated Drug Interaction

The following cytochrome P450 (CYP) enzymes are recommended for routine assessment to identify potential P450-mediated drug interactions: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Evaluation of phase II enzymes is highly encouraged if applicable (6).

Understanding Whether an NME is a Substrate for a Particular P450 Enzyme

Understanding which P450 enzyme is responsible for the metabolism of an NME is important in the evaluation of drug interaction potential. Drug interaction is likely to occur between such a drug and known inhibitors or inducers of that specific pathway if it contributes >25% to the total clearance of the NME. It is also important for selecting the interacting drugs to evaluate drug interaction *in vivo*, determining the impact of polymorphic enzyme activity on drug disposition, and deciding whether a multiple inhibitor study may be warranted. In general, the likelihood of drug interactions increases when a compound has a high affinity for a single metabolizing enzyme compared with a compound with affinity for a number of different enzymes.

A set of experiments (also known as reaction phenotyping) is conducted to identify the specific enzymes responsible for the metabolism of an NME. Oxidative and hydrolytic reactions involve cytochrome P450 (CYP) and non-CYP enzymes. For many drugs, transferase reactions (involving phase II enzymes) are preceded by oxidation or hydrolysis of the drug. However, direct transferase reactions may represent a major metabolic pathway for compounds containing the requisite functional groups. The guidance recommends that

the metabolic profile of the NME be investigated using human liver tissues such as freshly isolated liver slices, freshly prepared or cryopreserved human hepatocytes, subcellular liver tissue fractions such as liver S9 fraction, liver microsomes, or recombinant complementary DNA (cDNA)-expressed microsomes for a particular CYP enzyme. If human *in vivo* data indicate that CYP enzymes contribute >25% of the total clearance of the NME, studies should be conducted using human liver microsomes or recombinant enzymes to determine the individual CYP enzymes responsible for the drug's metabolism. If an NME is a substrate of a particular CYP, an *in vivo* interaction with a strong inhibitor or inducer for that CYP is needed to determine whether inhibition or induction of this particular pathway may lead to a change in the NME's pharmacokinetics. Negative results would alleviate further *in vivo* studies with less strong inhibitors or inducers. If results are positive, further clinical studies with less potent inhibitors or inducers would generally be needed to provide guidance on dosage adjustment.

If an NME is metabolized by a polymorphic enzyme (such as CYP2D6, CYP2C9, or CYP2C19), the extent of drug interactions (inhibition or induction) may be different depending on the subjects' genotype for the specific enzyme being evaluated. For example, subjects lacking the major, polymorphic clearance pathway will show reduced total metabolism. But alternative pathways may become quantitatively more important and need to be understood and studied appropriately. In general, the comparison of pharmacokinetic parameters of this NME in poor metabolizers *versus* extensive metabolizers may indicate the extent of interaction of this drug with strong inhibitors of these enzymes and make interaction studies with such inhibitors unnecessary. When the above study shows significant interaction, further evaluation with weaker inhibitors may be necessary.

Understanding Whether an NME is an Inhibitor for a Particular P450 Enzyme

If an NME is an inhibitor of a specific CYP enzyme, it may have the potential to inhibit the metabolism of a substrate drug of that CYP enzyme. The inhibition potential is usually evaluated using human liver microsomes or cDNA-expressed microsomes. An *in vitro* inhibition constant (K_i) that reflects the inhibitory effect of the NME is determined and its value is compared to clinically relevant concentrations. Because hepatocyte concentration is not easily measured, plasma concentrations are often used for this estimation. For an NME as a reversible inhibitor for a particular CYP enzyme, the guidance suggests that *in vivo* inhibition studies with representative substrates for that enzyme are needed if the calculated $[I]/K_i$ is >0.1, where $[I]$ is the estimated mean maximum total (bound and unbound) plasma concentration (C_{max}) at steady state of the highest clinical dose and K_i is the inhibition constant for the NME measured *in vitro*. The total plasma concentration (instead of the free plasma concentration) is used as a conservative estimate to predict the expected higher hepatic concentration and to avoid false negative results when free plasma concentration is used in the I/K_i calculation. When evaluating the potential of the NME to inhibit CYP3A, at least two structurally different CYP3A substrates such as midazolam and testosterone should be used

(8,9). If the $[I]/K_i$ is >0.1 from either substrate, an *in vivo* interaction study is recommended.

In addition, time-dependent inhibition (TDI) potential for an NME should be evaluated. TDI is a collective term for a change (often an increase) in potency of CYP inhibitors during *in vitro* incubation or dosing period *in vivo*. Potential mechanisms include the formation of a more inhibitory metabolite or mechanism-based inhibition: the inactivation of enzymes by metabolic products that form haem or protein adducts. Over the past decade, time-dependent CYP inhibition has been recognized to be responsible for some important drug interactions *in vivo* (10). For example, the calcium channel blocker, mibefradil, is a potent mechanism-based CYP3A inhibitor and P-glycoprotein (P-gp) inhibitor (11). Mibefradil was withdrawn in 1998 shortly after its approval as a consequence of serious drug–drug interactions with substrates of CYP3A and/or P-gp (11,12). Therefore, TDI should be studied and its possible *in vivo* drug interaction potential needs to be projected.

Time-dependent inhibition is mainly assessed *in vitro* using microsomes or hepatocytes and has been incorporated increasingly in drug discovery process (13,14). Although inhibition parameters (i.e., k_{inact} and K_I) can be readily obtained *in vitro*, prediction of time-dependent inhibition *in vivo* remains challenging because of the complexity of the mechanism as compared to reversible inhibition. Thus, a decision tree with regard to the evaluation of mechanism-based inhibition *in vivo* based on *in vitro* parameters similar to the evaluation of reversible inhibition outlined in the FDA draft guidance needs to be developed.

Understanding Whether an NME is an Inducer for a Particular P450 Enzyme

An NME that induces a CYP enzyme can cause drug interactions with substrate drugs for that particular pathway leading to enhanced clearance. Human primary hepatocytes are the preferred experimental system for the evaluation of P450 induction. The results of a recent survey of the practice in pharmaceutical industries indicated general consensus that human hepatocyte culture induction studies are the best predictor of *in vivo* induction (15). However, there appeared to be no standard methods for conducting these studies and no consistent criteria for determining whether a clinical drug–drug interaction study should be carried out (15). The FDA guidance suggests that induction studies be carried out using freshly isolated or cryopreserved human hepatocytes or immortalized cell lines including a positive control. Hepatocytes need to be prepared from at least three individual donor livers because of the known inter-individual differences in induction potential. When using immortalized cell lines, the experiment needs to be conducted in triplicate. If the increase in enzyme activity for NME-treated cells is $>40\%$ of a positive control in any one batch of hepatocytes or immortalized cell lines, the NME is considered to be an enzyme inducer and *in vivo* induction studies are recommended. An alternative endpoint is the use of an EC_{50} (effective concentration at which 50% maximal induction occurs) value, an index that can be used to compare the potency of different compounds. Relative induction score approach has also been reported for prediction of induction potential (16).

Studies have indicated that activation of the nuclear receptor, pregnane X receptor, results in the co-induction of CYP3A and CYP2C. Thus, a negative *in vitro* result for CYP3A induction may eliminate the need for additional induction studies for both CYP3A and CYP2C enzymes. However, whether CYP2C and CYP3A are always co-induced may need further validation. Because CYP1A2 induction is mainly via aryl hydrocarbon receptor (AhR), CYP1A2 is not likely to be co-induced with CYP3A. For CYP2B6, although overlap exists between CYP2B6 and CYP3A inducers, there are data suggesting that certain CYP2B6 inducers selectively bind to the constitutive androstane receptor (CAR), and these inducers do not show significant induction for CYP3A (17). Therefore, the potential for induction of CYP1A2 and CYP2B6 should be evaluated separately regardless of the CYP3A induction result.

Phase II Enzymes

Phase II enzymes have been recognized to play important roles in the pharmacokinetics of drugs. Historically, these enzymes have attracted less attention than CYP enzymes in drug interaction potential evaluation, most likely due to the lack of tools to study them and/or a lower incidence of observed adverse drug–drug interactions. Exceptions include the polymorphisms of *N*-acetyltransferases (18) resulting in fast and slow acetylators and acyl glucuronidation by UDP glucuronosyl transferases (UGTs) (19); both can lead to the formation of toxic metabolites. Recently, there has been an increased interest in drug–drug interactions involving UGTs. For example, polymorphism of UGT1A1 was shown to affect exposure of SN-38, an active metabolite of irinotecan, which has efficacy and safety implications (20,21).

Similar to the CYP enzymes, UGTs are encoded by a UGT gene “superfamily” with 17 human UGT proteins identified to date (22). Unlike CYP enzymes, there is no consensus with respect to the tools, i.e., enzyme sources, selective substrates, inhibitors, and inducers for studying the UGT enzymes. Recombinant human UGTs, many are available from commercial sources, have been used to investigate the individual UGT enzymes responsible for the formation of a drug glucuronide metabolite. UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 are considered to be the enzymes of the greatest importance in hepatic drug elimination (Zhang Y., *et al.*, book chapter submitted).

Establishing *in vitro*–*in vivo* correlation for drugs that are eliminated by glucuronidation has been challenging as compared to CYP enzymes. For example, the use of microsomes to determine the intrinsic clearance of drugs that are eliminated by glucuronidation is problematic because UGTs are integral proteins of the endoplasmic reticulum and are dependent on lipid for catalytic activity; both are variable parameters not controlled well in *in vitro* system.

Prediction of Transporter-Mediated Drug Interaction

In addition to the effects of drug metabolizing enzymes on the pharmacokinetics of drugs, increasing attention is being given to transporters where emerging evidence indicates their important role in modulating drug absorption,

distribution, metabolism, and elimination as well as the historical importance of transporters in the development of drug resistant tumors. Transporters, acting alone or in concert with drug metabolizing enzymes, can affect the pharmacokinetics and/or pharmacodynamics of a drug. Of the various transporters, P-gp is the most well and extensively studied transporter.

Understanding Whether an NME is a Substrate for P-gp

To test whether the NME is a P-gp substrate, bidirectional experiments of cell transport are carried out with the NME to determine the net flux ratio for the basolateral to apical (B→A) and apical to basolateral transport (A→B). If the efflux ratio, (B→A) to (A→B), is ≥ 2 and addition of P-gp inhibitors to the experiment decreases the net flux ratio by more than 50% or decreases the ratio to close to 1, then the NME is a potential P-gp substrate. A net flux ratio “cutoff” higher than 2 or a relative ratio to positive controls may be used to avoid false positives if a ratio of 2 is deemed non-discriminative as supported by prior experience with the cell system used. If *in vitro* experiments demonstrate that an NME is a P-gp substrate, additional drug-specific factors may be considered before determining whether an *in vivo* drug interaction study is warranted. For example, the bioavailability of the Biopharmaceutics Classification System Class 1 (23) or the Biopharmaceutics Drug Disposition Classification System Class 1 (24) NMEs that are highly soluble, highly permeable, and highly metabolized may not be significantly affected by a co-administered drug that is a P-gp inhibitor, and thus, an *in vivo* interaction study may not be needed. Nonetheless, it is recognized that the effects of P-gp inhibitors at the tissue levels (e.g., tumor or brain) cannot be easily assessed. If an NME is a substrate for both CYP enzyme and transporter, selection of inhibitors for studying inhibition needs to consider the significant overlap between enzymes and transporters (e.g., CYP3A and P-gp). A “dual” inhibitor for enzyme and transporter may be selected to study the maximal inhibition effect, although specific attribution of an AUC change to transporter or CYP enzyme may not be possible.

For NME that has low cell permeability due to lack of basolateral transporters in the cell lines for P-gp evaluation, the use of membrane vesicles may be an alternative method to understand the “intrinsic” affinity of NME to P-gp.

Understanding Whether an NME is an Inhibitor for P-gp

To test whether the NME is a P-gp inhibitor, bidirectional experiments of cell transport are carried out after adding varying concentrations of the NME to both sides of the monolayer followed by adding known P-gp substrates to the apical or basal side of the monolayer. The NME is a potential P-gp inhibitor if the net flux ratio of a P-gp probe substrate is decreased in the presence of the NME. To determine the potency of inhibition, an IC_{50} (concentration that inhibits 50%) or K_i value is determined.

The criteria for determining whether an *in vivo* drug interaction study is needed are evolving. The draft guidance published in Sept 2006 recommends $[I]/IC_{50}$ of 0.1 as the “cutoff” for further *in vivo* evaluation, where $[I]$ represents

the total C_{max} (bound plus unbound) at steady state at the highest clinical dose for NME (6). This ratio was adopted from criteria used to determine whether an NME is an inhibitor of P450 metabolizing enzymes. In contrast to P450 enzymes in the liver or transporters in the kidney where $[I]$ reflects the systemic C_{max} , $[I]$ concentrations at the luminal side of GI may be more relevant when evaluating P-gp inhibition by the NME following oral administration.

To provide better criteria for recommending *in vivo* inhibition studies, *in vitro* IC_{50} (or K_i) values and *in vivo* inhibition data for marketed drugs and drugs under development, using the prototypic P-gp substrate digoxin, were collected and evaluated (25). Based on the evaluation results, the following alternative criteria are proposed: drugs that exhibit an $[I]_1/IC_{50} > 0.1$ or $[I]_2/IC_{50} > 10$ should be evaluated *in vivo* to determine whether there is clinically relevant P-gp inhibition with digoxin, a P-gp substrate with a narrow therapeutic index, where $[I]_1$ is the mean NME steady-state total C_{max} at the highest clinical dose and $[I]_2$ is the theoretical maximal gastrointestinal NME concentration after oral administration estimated by the ratio of the highest clinical dose (mg) to a volume of 250 mL. If an NME meets either criterion, an *in vivo* drug interaction study with digoxin is recommended. Results from a recent publication from Fenner *et al.* (26) indicate that the proposed criteria for *in vivo* P-gp inhibition evaluation are reasonable.

Studying P-gp inhibition with digoxin is clinically relevant and useful because digoxin has a narrow therapeutic index and is one of the few known P-gp substrates that is not a CYP3A substrate. As more information about the interplay of P-gp and CYP3A emerges, the clinical relevance of P-gp may be better understood. Inhibition data obtained with digoxin may be applied to other “pure” P-gp substrates that have a narrow therapeutic index.

It is important to recognize the limitations of only using *in vitro* IC_{50} to predict *in vivo* interactions mediated by P-gp inhibition. The *in vitro* IC_{50} determination may be different across different laboratories. Appropriate controls are needed to compare results from different laboratories. Continued data collection is needed to further evaluate the adequacy of these criteria to predict possible *in vivo* interactions mediated by P-gp. A working group was formed following the October 2008 Transporter Workshop to continue further research in the area towards better predicting *in vivo* P-gp-mediated interaction based on *in vitro* data (Dr. Caroline Lee, personal communication).

Understanding Whether an NME is an Inducer for P-gp

Methods for *in vitro* evaluation for P-gp induction are not well understood. Thus, the P-gp induction potential of an investigational drug can only be evaluated *in vivo*. Because of similarities in the mechanism of CYP3A and P-gp induction, information from tests of CYP3A inducibility can inform decisions about the induction P-gp. If an NME is found not to induce CYP3A *in vitro*, no further tests of CYP3A and P-gp induction *in vivo* are necessary. If a study of the NME’s effect on CYP3A activity *in vivo* is indicated from a positive *in vitro* screen but the drug is shown not to induce CYP3A *in vivo*, then no further test of P-gp induction *in vivo* is necessary. However, if the *in vivo* CYP3A induction test is positive, then

an additional study of the NME's effect on a P-gp probe substrate is recommended (6).

Evaluation of Transporters Other Than P-gp

Reports of drug disposition mediated by membrane transporters other than P-gp continue to appear in the literature. For example, OATP1B1 and NTCP may play a major role in the disposition of the HMG-CoA reductase inhibitor rosuvastatin (27,28). A recent clinical study demonstrated that a genetic variation in the hepatic uptake transporter OCT1 is a determinant of metformin pharmacokinetics and may be associated with variation in response to this drug (29,30). Drug interaction potential exists if an NME is a substrate or inhibitor/inducer of transporters. However, routine *in vitro* studies cannot be recommended for transporters other than P-gp at this time because no consensus has been reached with regard to *in vitro* methods or probe substrates and inhibitors. Until additional knowledge and technologies are available, recommendations for evaluation of transporter-based drug interactions other than P-gp (e.g., OATP, BCRP, OATs, and OCTs) are on a case by case basis.

A recent DIA/FDA Critical Path Transporter Workshop has discussed the emerging science in transporters (7). An international working group, including members from academia, industry, and the FDA, are working on a whitepaper to highlight the recent progress in this field including *in vitro* tools and criteria for *in vivo* drug interaction evaluation for main transporters including P-gp, BCRP, OATP, OCT, and OAT.

In Silico Models

The current FDA guidance uses criteria that are based on *in vitro* K_i values in combination with *in vivo* total plasma/blood concentrations to predict the likelihood of drug interactions for NMEs as CYP inhibitors. The limitations of the I/K_i approach have been discussed elsewhere (31–36). For example, using total $[I]$ may over-predict for drugs that are highly protein-bound in plasma. Conversely, using unbound plasma $[I]$ may under-predict for drugs that are highly concentrated in the liver by uptake transporters (37). The use of single inhibitor concentration also poses a potential limitation because the *in vivo* drug interactions are expected to be dependent on the pharmacokinetic characteristics of both inhibitor and substrate.

Over the years, *in vitro* to *in vivo* prediction models have been developed to predict/simulate the magnitude of the interaction based on *in vitro* results (16,38–41). Commercial software products have been developed as well. Time–concentration profile and/or inter-individual variability of intrinsic factors influencing ADME processes of both substrate and inhibitor drugs based on physiological-based pharmacokinetic prediction approach have been integrated into the modeling algorithm (38,39,42–45). Modeling and simulation of drug interactions *in vivo* using the physiological-based pharmacokinetic approach appear to be valuable in evaluating the magnitude of drug interaction potential under different clinical scenarios, e.g., different dosing regimen (44,46,47). The tools are helpful not only in

interaction prediction but also in clinical study design. Although progresses have been made in the *in silico* models to predict drug interactions, challenges remain because the lack of the true physiological representation in the models limits the ability to predict *in vivo* situations such as enzyme and transporter interplay at various tissues, e.g., different interplay of CYP3A4 and P-gp in the intestine vs. in the liver.

Recent NDA Examples

Recent IND and NDA reviews indicate that most pharmaceutical companies conduct recommended *in vitro* evaluation studies according to the guidance prior to drug approval. For example, a recent review of 121 new molecular entity drugs approved during 2003 and 2008 (up to Dec. 21, 2008) indicated that 88% (57 out of 65) of those intended for oral administration included *in vitro* study information with regard to which metabolic and/or transport pathways are involved in the ADME process of the drug (Fig. 1) (48). P450 3A is the main P450 enzyme involved in the metabolism of NMEs. In addition, most NMEs were studied for their inhibition or induction potential for major P450 enzymes. The information has greatly enhanced our ability to predict *in vivo* interaction potential to construct an informative labeling. Besides major CYPs and P-gp, *in vitro* evaluation studies are increasingly conducted with regard to whether an NME is a substrate or inhibitor for phase II enzymes (mostly UGTs) and transporters other than P-gp (e.g., BCRP, OATP1B1, OAT, and OCT). Although *in vitro* studies are being conducted, we found that positive *in vitro* findings are not necessarily always followed by *in vivo* drug interaction evaluation. In these situations, appropriate language is usually constructed in the labeling based on *in vitro* results. In some cases, post-marketing drug interaction studies are requested according to clinical need.

For example, ambrisentan, an endothelin receptor antagonist, was approved in 2007 for the treatment of pulmonary arterial hypertension (48). It was found to be a substrate of CYP3A, CYP2C19, UGT1A9, UGT2B7, UGT1A3, OATP, and P-gp. Because the relative contribution of each pathway

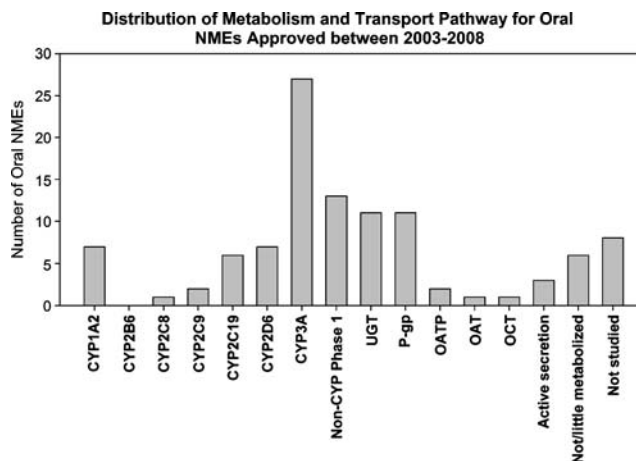


Fig. 1. Distribution of metabolism and transport pathways for NMEs approved between 2003 and 2008 intended for oral administration

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