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In Vitro-In Vivo Extrapolation of Metabolism- and Transporter-Mediated Drug-Drug Interactions – Overview of Basic Prediction Methods

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**List of abbreviations:**

ADME: absorption, distribution, metabolism and excretion  
BCRP: breast cancer resistance protein  
CYP: cytochrome P-450  
d: induction calibration factor  
DDI: drug-drug interaction  
EC$_{50}$: concentration of inducer associated with half-maximum induction  
EMA: European Medicines Agency  
$E_{\text{max}}$: maximum induction effect  
$F_d F_g$: intestinal bioavailability  
FDA: Food and Drug Administration  
f$_{u,p}$: fraction unbound in plasma  
[I]: perpetrator (inhibitor or inducer) concentration  
$I_{\text{max}}$: maximum total (unbound plus bound) inhibitor concentration in plasma  
$I_{\text{max},u}$: maximum unbound inhibitor or inducer concentration  
ITC: International Transporter Consortium  
$I_{u,in,max}$: theoretical maximum unbound hepatic inlet concentration  
IVIVE: in vitro-in vivo extrapolation  
k$_a$: absorption rate constant  
k$_{\text{deg}}$: degradation rate constant of CYP enzyme  
$K_i$: inhibition constant  
$K_{\text{iact}}$: apparent inactivation constant  
$k_{\text{iact}}$: maximal inactivation rate constant  
k$_{\text{obs}}$: the apparent inactivation rate constant  
MATE: multidrug and toxin extrusion protein  
OAT: organic anion transporter  
OATPs: organic anion transporting polypeptides  
OCT: organic cation transporter  
PET: positron emission tomography  
P-gp: P-glycoprotein  
PK: pharmacokinetic  
PMDA: Pharmaceuticals and Medical Devices Agency of Japan  
$Q_h$: hepatic blood flow rate  
$R_q$: blood-to-plasma concentration ratio  
RIS: relative induction score  
UGT: UDP-glucuronosyltransferase
Abstract

Evaluation of drug-drug interaction (DDI) risk is vital to establish benefit-risk profiles of investigational new drugs during drug development. In vitro experiments are routinely conducted as an important first step to assess metabolism- and/or transporter-mediated DDI potential of investigational new drugs. Results from these experiments are interpreted, often with the aid of in vitro-in vivo extrapolation (IVIVE) methods, to determine whether and how DDI should be evaluated clinically to provide the basis for proper DDI management strategies, including dosing recommendations, alternative therapies, or contraindications under various DDI scenarios and in different patient population. This article provides an overview of currently available in vitro experimental systems and basic IVIVE methodologies for metabolism- and transporter-mediated DDIs.

1 Background

Many factors can affect pharmacokinetic (PK) profiles of drugs after administration to different patients, including concomitant medications, disease status, and genetic polymorphisms. For optimal use of medications, it is important to understand which factors are relevant to the pharmacokinetics of each drug. DDIs are one of the important factors that alter the pharmacokinetics of drugs, and they have in some cases resulted in fatal adverse events leading to withdrawal of drugs from the market. Because of their importance, the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Ministry of Health, Labour and Welfare of Japan (MHLW) have published a draft guidance or guideline (FDA and MHLW) or a final guideline (EMA) on methodologies to evaluate DDIs for investigational new drugs during drug development. The evaluation of DDIs generally involves multiple processes, including 1) prediction of clinical DDIs with preclinical or in vitro systems, 2) evaluation/confirmation of the extent of DDIs with clinical studies, and/or 3) model-based simulations of DDIs. This review article focuses on the first element, prediction of DDI using data from preclinical and in vitro systems, especially focusing on basic IVIVE methodologies.

2 Clinically relevant metabolizing enzymes and transporters for DDI evaluation

The most well-known and important proteins involved in PK-based DDIs are enzymes of the cytochrome P-450 (CYP) family. The inhibition or induction of CYP enzymes can directly affect the exposures to substrate drugs and result in unexpected changes in efficacy and/or safety profiles without appropriate dose adjustment. Many of CYP enzymes have broad substrate specificity and they mediate the metabolism of the majority of marketed small molecule drugs. Clinically important CYP enzymes relevant for PK-based DDIs include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Many of these CYP enzymes are predominantly expressed in the liver. CYP3A is also expressed significantly in the intestine and it can contribute to the intestinal first-pass extraction of orally administered drugs. Other drug metabolizing enzymes, such as UDP-glucuronosyltransferase (UGT), are less frequently evaluated for potential PK-based DDIs, mainly due to the lack of selective inhibitor and inducer drugs that can significantly influence PK of their substrates.

In contrast to drug metabolizing enzymes, the alteration of transporter function can not only affect drug elimination, but also drug distribution. For example, inhibition of organic anion transporting polypeptides (OATPs) by rifampin significantly reduces radioactivity measured in the
liver with positron emission tomography (PET) after the administration of (15R)-11C-TIC-Me in humans\textsuperscript{6} or rosvastatin in rats\textsuperscript{7}. A list of drug transporters that may alter drug disposition has been recommended by the International Transporter Consortium (ITC)\textsuperscript{8-11}. Drug transporters that may be involved in clinically significant DDIs include OATP1B1/OATP1B3, organic anion transporter 1/3 (OAT1/OAT3), organic cation transporter 2 (OCT2), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), and multidrug and toxin extrusion protein 1/2-K (MATE1/MATE2-K). The regulatory agencies from the U.S., Europe, and Japan adopted this recommended list in their recently published DDI guidance/guidelines\textsuperscript{2-4}.

3 In vitro experimental systems

The gold standard for preclinical DDI evaluation has been the use of enzyme- or transporter-expressing systems or human cellular and subcellular fractions. Because of species differences in metabolizing enzymes and transporters between human and animals, results of DDI studies in animals are not frequently used to predict clinical DDIs. In general, the purpose of using human expression systems is to evaluate specific interaction of one particular human protein with the drug of interest. Use of holistic cellular systems (e.g., hepatocytes) allows characterization of the relative contribution of individual metabolizing enzymes or transporters to the drug clearance in the presence of all other proteins. In this section, we briefly explain available in vitro experimental systems for DDI evaluation, focusing predominantly on the inhibition type interactions. More detailed descriptions of individual experimental systems can be found in other review articles\textsuperscript{12,13}.

Human liver microsomes and human hepatocytes are the most commonly utilized human in vitro systems to evaluate metabolism-mediated DDI. In many cases, in vivo metabolism pathways of a drug can be effectively evaluated with these systems. Probe substrates, inhibitors and inducers for individual CYP enzymes have been well established\textsuperscript{14,15} allowing the evaluation of DDI potential for an investigational drug with these systems with the drug acting either as a substrate or as a perpetrator. Microsomes prepared from cells overexpressing a specific isoform of enzyme (e.g., recombinant CYP enzymes) are useful to determine the involvement of a specific enzyme to the metabolism of the investigational drug and can be applied for evaluation of DDIs (hepatic and intestinal).

Compared to metabolism-mediated DDIs, cell lines transfected with individual transporters (e.g., HEK-OATP1B1) are used more frequently for the evaluation of transporter-mediated DDIs. The system of choice depends on questions of interest, function and directional characteristics of transporters\textsuperscript{13,16,17}. Transfected cell lines expressing individual transporters of interest, coupled with probe substrates, are useful for studying a drug as a potential transporter inhibitor. When evaluating the drug as a potential substrate, these systems address a “yes/no” question to determine the involvement of a particular transporter. Human hepatocytes express multiple transporters and are useful tools to determine quantitative contributions of a transporter, investigate rate limiting processes, and complex metabolism-transporter interplay\textsuperscript{13}.

Certain methodological aspects of transporter in vitro inhibition studies are still challenging and may affect ability to predict transporter-mediated DDI risk. For example, selective probe substrates and inhibitors for each transporter have not been well established. Occurrence of substrate-dependent inhibition, associated with possible multiple binding sites, highlights the need to use relevant substrate co-medications/clinical probe in the in vitro inhibition studies\textsuperscript{16}. Some OATP inhibitors (e.g., cyclosporine) have shown increased inhibitory potency following a pre-incubation step\textsuperscript{18,19}. In addition, quantitative estimation of inhibition parameters may require mathematical modeling of in vitro data. This is of particular relevance for the efflux transporters, as the interaction
of these transporters with the unbound intracellular drug concentration is considered in the model, rather than the nominal incubation concentration\textsuperscript{16}. Furthermore, large inter-laboratory variations have been reported for in vitro inhibition parameters (IC\textsubscript{50} values) for certain transporters (e.g., OATP1B1 and P-gp) \textsuperscript{20,21}. This may require additional effort for successful IVIVEs, such as standardization of in vitro methods or calibration of cellular systems using a standard set of model inhibitors, as discussed in digoxin case\textsuperscript{22} to generate “customized” decision criteria for DDI prediction.

4 In vitro-in vivo extrapolation of DDI

The next step of DDI evaluation is the extrapolation of in vitro parameters to in vivo interaction predictions. For a new drug as a substrate, knowing the contribution of a specific metabolizing enzyme or transporter to the overall absorption, distribution, metabolism and excretion (ADME) processes, based on IVIVE and clinical PK data, is required for an effective evaluation of clinical DDI potential. For example, in the case of a metabolism-based DDI, it is recommended to conduct a clinical DDI study with strong index inhibitors and/or inducers if an enzyme of interest is responsible for $\geq25\%$ of the drug’s elimination based on in vitro phenotyping and human PK data.

For a new drug as a perpetrator, the first step of extrapolation is often a simple comparison of in vitro parameters with in vivo exposure to the drug (also known as a basic model). If a basic model shows the potential of clinical DDI according to a predefined cut-off criterion, the interaction potential may be usefully investigated via a clinical DDI study or with the use of mechanistic models such as physiologically-based pharmacokinetic (PBPK) models\textsuperscript{2-4}. In the following sections, we provide an overview of the basic models for evaluating metabolism- and transporter-mediated DDIs involving a new drug as a perpetrator.

4.1 Prediction of metabolism-mediated DDI

The essential components of any metabolism- and transporter-mediated DDI predictions are the estimation of perpetrator concentration at the site of interaction and the in vitro potencies of the perpetrator (defined by inhibition constant, $K_i$). A basic model uses a constant value of perpetrator concentration to simplify prediction calculations. In many cases, the maximum steady-state concentration of the perpetrator at the highest clinical dose is used to minimize the likelihood of false negative prediction during this first step of evaluation. Basic models include other simplifications, such as assumption of 100\% involvement of the pathway of interest, no consideration of the interplay of multiple enzymes or transporters and use of plasma concentration as a surrogate of the perpetrator concentration at the site of interaction\textsuperscript{16}. The majority of metabolism-mediated DDI predictions focus on CYP-mediated interactions due to their clinical significance. Prediction methods for other enzymes such as UGTs have not been well established.

For reversible inhibition, the basic model uses a simple comparison of the inhibitor concentration and the $K_i$ for inhibitor-enzyme of interest. There are differences in the recommendations by regulatory agencies on inhibitor concentrations and cut-off values to use: e.g., $I_{\text{max}}/K_i \geq 0.1$ (FDA recommendation in 2012 draft guidance\textsuperscript{2} and MHLW recommendation in 2014 draft guideline\textsuperscript{4}) and $I_{\text{max,u}}/K_i \geq 0.02$ (EMA recommendation in 2013 guideline\textsuperscript{5}), where $I_{\text{max}}$ and $I_{\text{max,u}}$ represent the maximum total (unbound plus bound) and unbound inhibitor concentrations in plasma, respectively. A recent analysis suggested that these two criteria performed similarly in predicting reported DDIs\textsuperscript{23}.

The above criteria are intended for the prediction of DDIs after drug reaches systemic circulation. The concentration of a potential inhibitor in the intestine following oral administration can
be much higher than the systemic concentration. Therefore, the prediction based on systemic concentration of inhibitor can underestimate interaction potential for orally administered drugs. The underestimation is especially of concern for substrates of CYP3A enzymes (and transporters such as P-gp or BCRP). Using dose/250mL as a surrogate for intestinal inhibitor concentration, a cut-off criterion of 10 for the (dose/250mL)/Ki, was proposed by regulatory agencies. This criterion was deemed appropriate based on analyses where performance of in vivo DDI prediction was assessed for CYP3A and P-gp using criteria similar to those in the guidances. The prediction criteria were recently evaluated using receiver operating characteristic analysis resulting in a higher intestinal [I]/IC50 cut-off, while tightening the criterion for systemic P-gp inhibition.

Prediction of the time-dependent inhibition (TDI) is more challenging than the reversible inhibition. The inherent difficulty is that dynamic changes in enzyme function due to inactivation are approximated with a simple, static equation. The parameters for basic models include degradation rate constant of CYP enzyme (kdeg), apparent inactivation constant (KI), and maximal inactivation rate constant (kinact). There are differences in the concentrations and cut-off criteria used for predictions among regulatory agencies. The following two equations are used for the basic model prediction of TDI of hepatic CYP enzymes:

- \((k_{obs}+k_{deg})/k_{deg} \geq 1.1\) where \(k_{obs} = k_{inact} \times I_{max}/(K_{I} + I_{max})\) (FDA 2012 draft guidance and MHLW 2014 draft guideline)
- \((k_{obs}+k_{deg})/k_{deg} \geq 1.25\) where \(k_{obs} = k_{inact} \times 50 \times I_{max,u}/(K_{I} + 50 \times I_{max,u})\) (EMA 2013 guideline)

where \(k_{obs}\) represents the apparent inactivation rate constant. A retrospective analysis demonstrated that neither equation resulted in any false-negative predictions. However, both equations led to positive predictions of inhibition for the majority of tested drugs, regardless of observed clinical DDI outcomes. Because of the time-dependent nature of TDI, a dynamic model-based approach provides a more reliable prediction of the extent of DDI with TDI. However, recent analyses highlight challenges in the prediction of complex metabolic DDIs, e.g., combined TDI and induction interactions, even when using mechanistic PBPK models. Furthermore, confidence in predicting complex transporter-metabolism interplay and associated DDIs is still generally low.

Several basic methods have been proposed for the prediction of enzyme induction. Proposed approaches with their respective threshold criteria include:

1) Fold-change method: mRNA increase ≥ a predefined threshold based on positive/negative controls and exceeds a certain % in comparison to positive controls. For example, EMA recommends a concentration-dependent mRNA increase of ≥100% (2-fold) and ≥20% of the response of the positive control in the presence of an investigational drug, at relevant concentrations stipulated in the guidance, as positive induction (EMA 2013 guideline);

2) Basic model: \(R_3 = 1/(1 + d \times E_{max} \times [I]/(E_{C50} + [I])) \leq 0.8\) as positive induction, where \(E_{C50}\) is the concentration of inducer associated with half-maximum induction, \(E_{max}\) is the maximum induction effect, \([I]\) is the inducer concentration, and \(d\) is the induction calibration factor;

3) Correlation method using \(I_{max,u}/E_{C50}\): Calculate \(I_{max,u}/E_{C50}\) values with cut-off values defined with known inducers and non-inducers; and

4) Correlation method using relative induction score, RIS: calibration of RIS (\(= E_{max} \times [I]/(E_{C50} + [I])\)) with known inducers.

Each regulatory guidance includes one or more of the above four methods for induction predictions. In addition to mRNA expression levels, induction can also be studied by assessing enzyme activities, with the caveat that induction may be masked by concurrent inhibition.
4.2 Prediction of transporter-mediated DDI

Basic models are the main prediction method used to extrapolate in vitro assessment of investigational drugs as potential in vivo transporter inhibitors. Because different transporters are expressed in different organs and different side of membranes, the accurate estimation of inhibitor concentrations at the site of inhibition is key for accurate predictions.

For OATP1B1 and OATP1B3, which are expressed at the basolateral membrane of hepatocytes, the basic prediction method uses the unbound hepatic inlet plasma concentration as the inhibitor concentrations. It is important to note that hepatic plasma concentration can be higher than systemic concentration after oral drug administration, because drugs absorbed from small intestine first reach the liver via portal vein. In order to account for the contribution of drug concentration from absorption, the following equation was proposed to estimate the theoretical maximum unbound hepatic inlet plasma concentration, $I_{u,in,max}$:

$$I_{u,in,max} = f_u \times (I_{max} + k_a \times \text{Dose} \times F_{a}F_{g}/Q_hR_B),$$

where $k_a$, $F_{a}$, $f_u$, $Q_h$, and $R_B$ represent absorption rate constant, intestinal bioavailability, fraction unbound in plasma, hepatic blood flow rate, and blood-to-plasma concentration ratio, respectively. Prediction accuracies of OATP-mediated DDIs using different inhibitor concentrations and different “cut-off” criteria have been compared in recent studies.

In the study by Vaidyanathan et al, $I_{u,in,max}/K_i \geq 0.1$, $I_{max,u}/K_i \geq 0.02$, and $I_{u,in,max}/K_i \geq 0.25$ alone (MHLW recommendation in 2014 draft guideline), or combined criterion $I_{max}/K_i \geq 0.1$ and $I_{u,in,max}/K_i \geq 0.25$ (FDA recommendation in 2012 draft guidance) were all considered reasonable to determine the need to consider conducting clinical DDI studies. Although there were small differences in numbers of false predictions among these criteria, it is important to note that different criteria led to different types of false predictions. For example, prediction using maximum plasma total (bound + unbound) concentration in the systemic circulation tends to cause false-positive predictions of highly protein-bound drugs. Therefore, it is important to consider differences between methods when interpreting prediction results, as described in detail in the publication by Vaidyanathan et al.

For renal transporters, OAT1/3, OCT2, and MATE1/2-K, proposed basic prediction methods use unbound maximum systemic concentrations of inhibitors. Compared to CYP enzymes or OATPs, there are fewer cases of renal transporter-mediated DDIs, and the degree of change in systemic concentration is relatively small, leading to a limited dataset for validation of basic prediction methods for renal transporters. Furthermore, OCT2 and MATEs often share the same substrates and inhibitors, therefore the net DDI effect may be affected by both transporters at the basolateral and apical side of the renal tubule cells. Thus, an accurate prediction of DDI is more challenging for substrates for OCT2 and MATEs and inhibition of both transporters may need to be considered simultaneously. It is also important to note that inhibition of MATEs may cause an increase of intracellular concentrations, which would not be reflected in the systemic exposure of substrate drugs. According to studies by Dong et al, for OAT1/3-mediated DDIs, two of the recommended criteria showed comparable prediction outcomes: $I_{max,u}/K_i \geq 0.1$ (FDA recommendation in 2012 draft guidance) and $I_{max}/K_i \geq 0.25$ (MHLW recommendation in 2014 draft guideline). For OCT2 and MATEs, they proposed to use a lower cut-off for MATEs (i.e., $I_{max,u}/K_i \geq 0.02$) than for OCT2 (i.e., 0.1, the same as that for OATs) because a lower cut-off appeared to avoid false negative prediction. Using a lower cut-off for MATEs also accounts for possible higher intracellular concentration of the inhibitor than its systemic concentration in the situation where the inhibitor is a substrate of an uptake transporter such as OCT2. Overall, because of the limited number of reported
DDIs and complex transporter interplays, the criteria for renal transporter-mediated DDIs need further evaluation.

P-gp and BCRP are expressed at various organs, but the main focus of DDI prediction for these transporters is on their inhibition in the intestinal lumen. One reason is that changes in oral bioavailability of substrate drugs by the inhibition of intestinal transporters can be reflected in the absorption profile of substrate drugs (e.g., \( C_{\text{max}} \) change). Another reason is that the inhibitor concentration is in general much higher in the intestine than in systemic circulation after oral dosing, thus more prone to the perpetrator effect\(^\text{18}\). In fact, modulation of these transporters at the systemic level is considered unlikely in clinical situations, because unbound systemic concentrations of marketed drugs are generally too low to exhibit significant inhibition\(^\text{40}\). For intestinal transporter-mediated DDI prediction, the same cut-off criterion as intestinal CYP3A (dose/250mL/K\(_i\) \( \geq 10 \)) is proposed by regulatory agencies\(^\text{2-4} \), as described earlier in the section 4.1.

5 Conclusions

In vitro experimental systems and basic prediction models have evolved as useful tools to evaluate the risk of metabolism- and transporter-mediated DDIs for new molecular entities. Depending on the site or mechanisms of interactions, various equations and decision criteria have been proposed for DDI predictions. Considering the importance of this first-step of DDI prediction, there has been an ongoing effort among FDA, EMA, and MHLW to harmonize the recommendations for DDI prediction involving both metabolizing enzymes and transporters\(^\text{23} \). It is important to note, however, that the focus of these simple prediction methods is to eliminate the need to further evaluate DDIs that are unlikely to cause significant PK changes by using conservative assumptions to minimize false-negative predictions. For a more accurate and quantitative prediction of DDIs based on in vitro observations, use of sophisticated model-based predictions such as PBPK modeling that incorporate mechanistic considerations of victim and perpetrator drug disposition should be explored, especially for DDIs involving multiple elimination pathways\(^\text{18,41} \).

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Conflict of interest/disclosure

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Figure Legend

Figure 1. Relationships between observed AUCR and different concentration of inhibitors divided by $K_i$ or IC$_{50}$. (a) $I_{\text{max}} / K_i$ or IC$_{50}$, (b) $I_{\text{max,u}} / K_i$ or IC$_{50}$, and (c) $I_{u,\text{in,max}} / K_i$ or IC$_{50}$. Each symbol represents one DDI case. Horizontal lines represent cut-off values for 5 basic prediction methods evaluated in the original study$^{21}$: (1) $I_{\text{max}} / K_i$ or IC$_{50} \geq 0.1$, (2) $I_{\text{max,u}} / K_i$ or IC$_{50} \geq 0.02$, (3) $R (= 1 + I_{u,\text{in,max}} / K_i$ or IC$_{50}) \geq 1.04$ (EMA$^3$), (4) $R (= 1 + I_{u,\text{in,max}} / K_i$ or IC$_{50}) \geq 1.1$, (5) $R (= 1 + I_{u,\text{in,max}} / K_i$ or IC$_{50}) \geq 1.25$ (MHLW 2014 draft$^4$), and (6) $I_{\text{max}} / K_i$ or IC$_{50} \geq 0.1$ AND $R \geq 1.25$ (combination of (1) and (5); FDA 2012 draft$^5$). AUCR: area under the concentration-curve ratio, DDI: drug-drug interactions, IC$_{50}$: half maximal inhibitory concentration, $I_{\text{max}}$: maximum systemic plasma concentration, $I_{\text{max,u}}$: maximum unbound systemic plasma concentration, $I_{u,\text{in,max}}$: estimated maximum inhibitor concentration at the inlet to the liver, $K_i$: inhibition constant, and OATP: organic anion transporting polypeptide. Figure from Vaidyanathan, et al., 2016$^{21}$.
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Figure 1

(a) $I_{\text{max}}/K_i$ or $IC_{50} \geq 0.1$

(b) $I_{\text{max, u}}/K_i$ or $IC_{50} \geq 0.02$

(c) $I_{u, \text{in, max}}/K_i$ or $IC_{50} \geq 0.04, 0.1, \text{or } 0.25$