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Clinical Drug-Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access

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List of abbreviations:

AE: Adverse event
AUC: Area under the concentration-time curve
CYP: Cytochrome P-450
CDER: Center for Drug Evaluation and Research
DDI: Drug-drug interaction
EMA: European Medicines Agency
E-R: Exposure-Response
FDA: Food and Drug Administration
PDUFA: Prescription Drug Users Fee Act
PK: Pharmacokinetic
PMDA: Pharmaceuticals and Medical Devices Agency of Japan
Abstract
Clinical drug-drug interactions (DDIs) can occur when multiple drugs are taken by the same patient. Significant DDIs can result in clinical toxicity or treatment failure. Therefore, DDI assessment is an integral part of drug development and the benefit-risk assessment of new therapies. Regulatory agencies including the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) have made recommendations in their DDI guidance documents on various methodologies (in vitro, in silico and clinical) to assess DDI potential and inform patient management strategies. This commentary focuses on clinical DDI evaluation for the purpose of drug development and regulatory evaluation.

Introduction
The clinical relevance of drug-drug interactions (DDIs) is clear: DDIs can increase the frequency and severity of adverse events (AEs) or increase the likelihood of treatment failure. DDI assessment is, therefore, a critical component of new drug development and regulatory evaluation. If DDI information is not available before the later stages of clinical development, segments of the target patient population that are on concurrent medication are often excluded from late-phase clinical trials (including trials with the expressed purpose of definitively establishing drug efficacy and safety). These exclusions may subsequently hinder generalizability of clinical trial results to the larger population of patients likely to receive the new drug after its approval. At the drug approval stage, it is challenging to provide instructions for DDI management in the prescribing information or product labeling if a drug’s potential for DDIs (either as a “substrate” or as a “perpetrator”) has not been appropriately evaluated. This lack of information can, in some cases, restrict the patient population that receives the drug and limit the access of patients to certain treatment options. At minimum, this knowledge gap can create challenges in the therapeutic use of a new drug. Thus, it is essential to identify and evaluate DDIs during drug development and determine appropriate strategies to manage them.

Empirical evidence of decreased efficacy or increased severity or frequency of AEs is the most clinically relevant measure of a DDI. However, it is not feasible to examine efficacy and safety for every potential DDI in clinical trials. Thus, establishing a mechanistic understanding of DDIs by performing a thorough in vitro evaluation is desired. In such cases, if in vitro studies reveal a potential for DDIs, subsequent clinical DDI studies or in silico PK-PD evaluations are recommended. From this information, it can be assessed whether clinically relevant DDIs may be best managed by staggering administration of the drugs, dosage adjustment or by contraindicating co-administration.
Clinical DDI studies generally use pharmacokinetic (PK) endpoints such as area under the concentration-time curve (AUC) or maximum concentration (C\text{max}), which allows drug developers to evaluate DDIs in smaller trials that can be executed in a timely manner without delaying approval of new medications or restricting drug access to patients on concomitant medications. However, observed DDI-mediated changes in PK should be put in context of the Exposure-Response (E-R) relationship in order to assess its impact on safety and efficacy. Knowledge of the E-R relationships for safety and efficacy evolve throughout the phases of drug development, with greater certainty as the drug progresses from early clinical trials to phase 3 trials and beyond. Thus DDI management strategies should consider the E-R relationship within the target population, the expected duration of co-administration, feasibility of dose adjustment, and availability of alternative treatments.

Overall, the goal of dose adjustments to manage DDIs is to achieve drug concentrations (exposure) that are deemed safe and effective based on prior clinical experience or E-R evaluations. Using this paradigm, one does not need to directly observe loss of efficacy or increase in frequency or severity of AE in a DDI study to determine whether a DDI is clinically relevant. It is sufficient to observe a change in drug exposure (typically on a population level) of a magnitude that would be associated with a worsening of benefit-risk. Because of the key role that clinical DDI studies play in patient care, they need to be designed and interpreted with scientific rigor. The remainder of this commentary describes the different types of clinical DDI evaluations and their respective purposes and limitations that are useful in drug development.

**Types of Clinical DDI Studies**

Clinical DDI studies are prospectively designed to determine both the presence and the magnitude of suspected DDIs. Detailed design issues related to DDI studies have been previously described and are beyond the scope of this commentary\textsuperscript{1-3}. In this commentary, we describe the purposes and limitations of different types of clinical DDI studies that are used in drug development.

**Stand-alone DDI studies**

**a. Index studies**

Index DDI studies use perpetrators (inhibitors or inducers) or substrates (victims) with well-known PK and DDI properties with regards to level of inhibition, induction, and metabolic pathway. The FDA maintains a list of recommended index perpetrators\textsuperscript{4} that: 1) have predictable effect-size, 2) are known to alter the function of a given metabolic or transporter pathway, and 3) are safe for use in healthy subjects. There is also a list of recommended index substrates\textsuperscript{4} that: 1) have a well understood contribution of a specific CYP pathway to their elimination, 2) have a well-defined interaction effect with index inhibitors.
and inducers, and 3) are safe for use in healthy subjects. For example, at the time of this publication, clarithromycin and itraconazole are included as the recommended strong index CYP3A4 inhibitors. A recent systematic review and meta-analysis 5 reported that both drugs have similar and predictable effect-size when administered with midazolam or triazolam (both are sensitive CYP3A4 index substrates) (Figure 1). In general, it is preferable to have data from several studies with different index substrates or index perpetrators for a drug to be classified as an index drug. However, there are other possibilities: e.g., an index substrate may be supported by clinical data that shows a clear effect of a well-defined genetic polymorphism on drug exposure.

Typical studies that use index inhibitors and inducers evaluate DDI potential in a controlled setting in healthy subjects. These studies are often stand-alone studies, with DDI evaluation as the primary objective. The purpose of these studies is to estimate the effect-size of a DDI under ‘worst-case conditions’. For drugs that are evaluated as victims of a DDI, the worst case is the concomitant administration of a strong index inhibitor or inducer of the drug’s major metabolic pathway(s). For drugs evaluated as perpetrators of DDIs, the worst case is the concomitant administration of the investigated drug with a sensitive index substrate, ideally at the highest dose level and most frequent dosing schedule of the investigated drug. Most studies evaluate univariate worst-case scenarios. Thus, the combination of several perpetrators or administration of perpetrators in a defined genetic subpopulation could result in larger effect-sizes, though the magnitude of such multi-factor considerations may not always be predictable given the reductionist nature of index studies.

A distinctive feature of index studies is that the results can be extrapolated to other drug combinations. As shown in Figure 1, the effect of clarithromycin is similar to the effect of itraconazole. Thus, after conducting a study with one index inhibitor one can assume that other index inhibitors of equal strength for that metabolic pathway will have similar DDI effect-size. Additionally, if one concludes that the change in drug exposure following a concomitant strong index perpetrator is not clinically relevant, the same can be concluded for all other strong inhibitors for that particular metabolic pathway, without the need of additional studies.

The FDA outlines its classification of the potency of inhibitors and inducers, and sensitivity of substrates for CYP enzymes in its guidance and on the FDA DDI website 4 (Tables 1 and 2). New drugs that are being evaluated as perpetrators in DDI studies can be classified as strong or moderate if the upper (or lower for inducers) 90% confidence interval reaches the threshold for the designation. For example, a drug that increases the AUC of a sensitive index substrate by more than 5-fold is designated as a strong inhibitor for that pathway. Designation of a drug as an index perpetrator requires a higher level of
evidence. Index perpetrators should consistently show that they reach the effect-size for moderate or strong perpetrators in several studies and preferably with several sensitive substrates.

**b. Concomitant use studies**

In contrast to index studies that seek to understand the worst-case scenario, concomitant use studies are studies that investigate DDIs between the investigated drug and drugs likely to be administered to the target population when the drug is approved. The choice of drugs to investigate in concomitant use studies should consider the relative frequency of co-administration as well as the mechanistic understanding of the potential for DDIs. The FDA provides a non-exhaustive list of approved drugs that are known strong or moderate perpetrators or sensitive or moderate sensitive substrates for specific metabolic pathways. Drug developers can use the list as a starting point and consider other drugs that may be more relevant to their target populations. While highly informative to patients and medical professionals, results from concomitant use studies can be difficult to extrapolate to other drugs. Because of a general lack of index substrates or perpetrators for transporter-mediated pathways, the choice of transporter substrates or perpetrators for DDI evaluation is often based on the likelihood of co-administration (i.e., to obtain clinically relevant DDI information that can inform labeling regarding the management of a DDI). As such, results from DDI studies that investigate transporter-mediated interactions are most relevant to the studied drugs and extrapolation of study results to other drugs is limited.

**Nested DDI Studies**

It is not necessary to conduct all clinical DDI evaluations in stand-alone studies in healthy subjects. DDIs can be evaluated as part of patient studies for which DDI evaluation is not the primary objective if the DDI evaluation plan is carefully designed. These nested studies have some advantages over DDI evaluations in small cohorts of healthy subjects; these include: 1) studies are conducted in a setting that more closely resembles “real world conditions”, 2) DDIs can cost-effectively be evaluated in a larger population, and 3) DDIs can be evaluated in a multivariate manner accounting for other patient factors such as renal function.

There are, however, challenges when designing nested DDI studies. Nested studies must be designed in a manner that is safe for study participants. For example, the expected effect-size of the interaction must be within upper safety concentration limits where known. It can therefore be difficult to study the effects of strong index inhibitors in nested studies for drugs that are unsafe to administer at doses well above the recommended dosage, unless it is possible to incorporate a dose adjustment. Another challenge is the dependence on patient reported dosing records in outpatient studies. For example, the effect of a non-time dependent inhibitor with a short half-life and limited accumulation on the PK of a substrate can be
sensitive to timing of the administration of the inhibitor and the substrate. As such, information on dosing records is critical for evaluating DDI in a nested study. Nested DDI studies often use population PK methods as the primary analysis for evaluating DDI. Important considerations on the conduct of clinical DDI studies and the utility of population PK have been elaborated earlier\textsuperscript{1-3,6-9}. Additionally, Bonate, et al. have outlined some technical and operational considerations for evaluation DDI using population PK methods\textsuperscript{10}.

**The Emerging Role of In Silico DDI Studies**

The use of model-informed drug development (MIDD) strategies has increased in the past few years\textsuperscript{11-13}. At the present time, several drug developers have submitted PBPK modeling and simulations to support the use of PBPK to inform clinical pharmacology study design and dosing recommendations for specific clinical scenarios (with concomitant medications, pediatric use, etc.). To reduce the number of unnecessary clinical DDI studies, while maximizing the DDI information, there is value in leveraging previously accumulated mechanistic understanding to make rational and scientific-based decisions. This principle is perhaps most evident in the use of in silico DDI studies that rely on PBPK models. PBPK models are mathematical summaries of the known human physiology that governs how the body interacts with drugs. Physiological and drug dependent aspects are included within these models. The physiological aspects of PBPK models, such as organ blood flows, transporter and CYP enzyme abundance levels, and their associated variability can be altered to simulate drug PK in specific patient groups. Likewise drug-dependent aspects including physiochemical properties (e.g., logP, molecular weight, etc.), and affinity to metabolizing enzymes, tissues, and proteins in the body can be leveraged as part of modeling a drug’s PK. The applications of PBPK in drug development and regulatory review, including evaluation of DDIs, are described in several publications\textsuperscript{14-20} and were the subject of a recent FDA advisory committee discussion\textsuperscript{21}. Table 3 shows application of PBPK models to predict DDI to support regulatory decisions and dosing recommendations, using clinical data from index DDI studies for model performance verification.
Conclusions

Multiple approaches and study-types can be used to evaluate the potential for DDIs throughout the new drug development process. To be most efficient and informative, mechanistic understanding of DDI potential and understanding of a new drug’s exposure-safety/efficacy properties should be considered in the design and interpretation of DDI studies. Application of these principles can permit timely development of DDI management strategies for integration into trial planning and eventual drug labeling. This information is critical to individualize patient care and avoid unnecessarily restricting patient access to new drugs because of important therapeutic knowledge gaps.

Acknowledgements

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References


Figure 1. Forest plot illustrating the effect-size of strong CYP3A index inhibitors on sensitive CYP3A index substrates. Studies are ordered by substrate and inhibitor combination and by precision of the point estimate. Each study result is represented by a box and error bars showing fold increase in AUC and 90% confidence interval (CI). The pooled results are illustrated by the black diamonds showing pooled fold increase in AUC and 90% CI estimated with the random-effects (RE) model. [modified from Sachar et al³]
<table>
<thead>
<tr>
<th>Change in AUC of a sensitive index substrate</th>
<th>Strong inhibitor</th>
<th>Moderate inhibitor</th>
<th>Strong inducer</th>
<th>Moderate inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ ≥ 5-fold</td>
<td>↑ ≥ 2- to &lt; 5-fold</td>
<td>↓≥ 80%</td>
<td>↓≥ 50% to &lt; 80%</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Classification of sensitive and moderate sensitive substrate for CYP enzymes.

<table>
<thead>
<tr>
<th>Change in AUC with a strong index inhibitor</th>
<th>Sensitive substrate</th>
<th>Moderate sensitive substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑ ≥ 5-fold</td>
<td>↑ ≥ 2- to &lt; 5-fold</td>
</tr>
</tbody>
</table>
Table 3. FDA-approved drugs for which PBPK analyses supported DDI-related regulatory decisions and dosing recommendations

<table>
<thead>
<tr>
<th>Drug Name (Approval Year)</th>
<th>Summary of simulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (2009)</td>
<td>Effect of ritonavir on sildenafil exposure</td>
</tr>
<tr>
<td>Cabazitaxel (2010)</td>
<td>Lack of CYP inhibition by cabazitaxel</td>
</tr>
<tr>
<td>Praziquantel (2010)</td>
<td>Effect of rifampicin co-administration</td>
</tr>
<tr>
<td>Ketoconazole (2010)</td>
<td>Lack of CYP inhibition by topically applied ketoconazole</td>
</tr>
<tr>
<td>Vilazadone (2011)</td>
<td>Similar drug interaction by ketoconazole under different dosing regimen</td>
</tr>
<tr>
<td>Rilpivirine (2011)</td>
<td>Similar drug interaction by ketoconazole at a lower dose of rilpivirine</td>
</tr>
<tr>
<td>Bosutinib (2012)</td>
<td>Support the need for a post-marketing study on effect of moderate CYP inhibitor</td>
</tr>
<tr>
<td>Perampanel (2012)</td>
<td>Similar drug interaction by ketoconazole under different dosing regimen</td>
</tr>
<tr>
<td>Ponatinib (2012)</td>
<td>The effect of rifampin on ponatinib exposure</td>
</tr>
<tr>
<td>Canagliflozin (2013)</td>
<td>Lack of CYP inhibition by canagliflozin</td>
</tr>
<tr>
<td>Simeprevir (2013)</td>
<td>Support of dosing recommendations under different drug interaction scenarios and in subjects with East Asian ancestry</td>
</tr>
<tr>
<td>Ibrutinib (2013)</td>
<td>Support of dosing recommendations for situations when ibrutinib is co-administered with various CYP modulators</td>
</tr>
<tr>
<td>Macitentan (2013)</td>
<td>Support of dosing recommendation for the effect of ritonavir on macitentan exposure</td>
</tr>
<tr>
<td>Naloxegol (2014)</td>
<td>Support of dosing recommendation for the effect of efavirenz</td>
</tr>
<tr>
<td>Eliglustat (2014)</td>
<td>Support of dosing recommendations for situations when eliglustat is co-administered with various CYP2D6 and CYP3A modulators in subjects with different CYP2D6 genotypes</td>
</tr>
<tr>
<td>Ruxolitinib (2014)</td>
<td>Support of dosing recommendations for situations when ruxolitinib is co-administered with fluconazole</td>
</tr>
<tr>
<td>Ceritinib (2014)</td>
<td>Support of dosing recommendations for situations when ceritinib is co-administered with CYP modulators at steady state</td>
</tr>
<tr>
<td></td>
<td>Support the need for a post-marketing study of the effect of food at a different dose of ceritinib</td>
</tr>
<tr>
<td>Rilpivirine (2014)</td>
<td>Support of dosing recommendation for the effect of a moderate CYP inducer on rilpivirine</td>
</tr>
<tr>
<td>Belinostat (2014)</td>
<td>Support of a post-marketing study on the effect of UGT polymorphisms</td>
</tr>
<tr>
<td>Compound</td>
<td>Description</td>
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<td>---------------------------------</td>
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<tr>
<td>Olaparib (2014)</td>
<td>Support of dosing recommendation for the effect of a moderate CYP inducer</td>
</tr>
<tr>
<td>Blinatumomab (2014)</td>
<td>Transient effect of “cytokine storm” on co-medications that are CYP substrate and supported duration of hospitalization for patients initiated with biologic treatment</td>
</tr>
<tr>
<td>Lenvatinib (2015)</td>
<td>The lack of drug inhibition effect on the PK of CYP3A and CYP2C8 substrates</td>
</tr>
<tr>
<td>Aripiprazole Lauroxil (2015)</td>
<td>Support of dosing recommendations for situations when the product is co-administered with various CYP modulators in subjects with different CYP2D6 genotypes</td>
</tr>
<tr>
<td>Cobimetinib (2015)</td>
<td>Support of dosing recommendations for co-medications that are CYP3A inducers</td>
</tr>
<tr>
<td>Dolutegravir (2015)</td>
<td>Support of dosing recommendations for co-medications that are UGT and/or CYP3A inducers</td>
</tr>
<tr>
<td>Sonidegib (2015)</td>
<td>Support of dosing recommendations for co-medications that are CYP3A modulators</td>
</tr>
<tr>
<td>Alectinib (2015)</td>
<td>Support of dosing recommendations for co-medications that are CYP2C8 substrates</td>
</tr>
<tr>
<td>Dasabuvir (2015)</td>
<td>Support of dosing recommendations for co-medications that affect CYP2C8</td>
</tr>
<tr>
<td>Crizotinib (2016)</td>
<td>Support of dosing recommendations for co-medications that are moderate CYP3A inducers</td>
</tr>
<tr>
<td>Guanfacine (2016)</td>
<td>Support of dosing recommendations for co-medications that are moderate CYP3A modulators</td>
</tr>
<tr>
<td>Temsirolimus (2016)</td>
<td>Support of dosing recommendations for co-medications that are CYP3A substrates</td>
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