U.S. FOOD & DRUG ADMINISTRATION

Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

Final Guidance for Industry

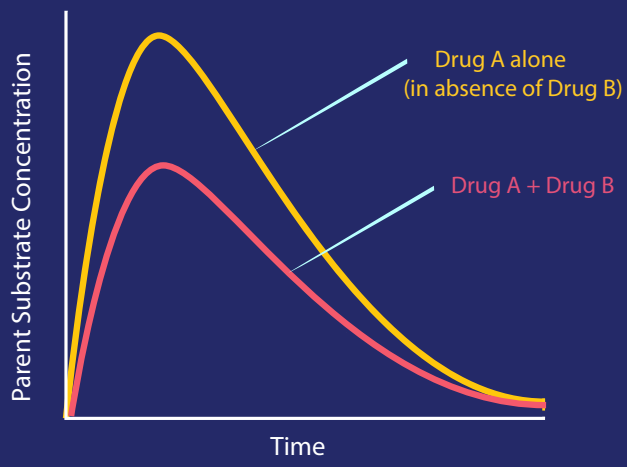
What is recommended in this guidance?

The final guidance Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions provides considerations for evaluating pharmacokinetic (PK) interactions mediated by cytochrome P450 (CYP) enzymes or transporters. The goals of studies that investigate CYP enzyme- and transporter-mediated drug interactions include the following:

- Determine whether the investigational drug alters the PK of other drugs
- Determine whether other drugs alter the PK of the investigational drug
- Determine the magnitude of changes in PK parameters
- Determine the clinical significance of the observed or expected drug-drug interactions (DDIs)
- Inform the appropriate management and prevention strategies for clinically significant DDIs

Clinical Drug Interaction Studies: compare drug substrate (victim) concentrations in the absence and presence of a potential perpetrator drug in vivo.

Parent Drug Substrate Concentration Results



Identified DDI

Interaction Due to Induction:

- Drug A is the victim[1] drug
- Drug B is the perpetrator[2] drug. Drug B causes a decrease in Drug A concentrations and, therefore, is an inducer.

1 The term victim refers to the drug whose exposure may or may not be changed by a perpetrator drug.

2 The term perpetrator refers to the drug that causes an effect on the victim (substrate) drug by inhibiting or inducing enzymes or transporters.

To learn more about clinical drug interaction studies, read the guidance:
https://www.fda.gov/media/134581/download

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Why is This Guidance Important?

Patients frequently use more than one medication at a time. Unanticipated, unrecognized, or mismanaged DDIs are an important cause of morbidity and mortality associated with prescription drug use and have occasionally caused the withdrawal of approved drugs from the market. This guidance provides recommendations for evaluating DDIs during drug development and determining essential information to communicate in labeling.

How Should Drug-Drug Interactions Be Presented in the Labeling?

The Prescribing Information should include a summary of essential DDI information, and the DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections of drug labeling should include the majority of the DDI information. When DDI information has direct implications for the safe and effective use of the drug, this information is often included in varying levels of detail in other sections of the labeling (e.g., BOXED WARNING, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and/or WARNINGS AND PRECAUTIONS sections), and must be discussed in more detail in the DRUG INTERACTIONS section (§ 201.57(c)(8)(i)).

Drug-Drug Interaction Studies: Prospective Studies vs. Retrospective Evaluations

Regulatory decision-making generally requires prospective studies specifically designed to detect DDIs as a major objective. Retrospective evaluation of drug concentrations from studies not designed to evaluate DDIs rarely includes sufficient precision to provide an adequate assessment.

Types of DDI Studies

Index Studies

To test whether an investigational drug is a victim of DDIs, sponsors should use index perpetrators. To test whether the investigational drug is a perpetrator, sponsors should use index substrates, which have defined changes in systemic exposure when administered with a strong inhibitor for a specific drug elimination pathway. A list of currently recommended index drugs for specific CYP pathways (either as substrates, inhibitors, or inducers) is maintained on the FDA's Web site for Drug Development and Drug Interactions.[3]

Concomitant-Use Studies

Sponsors should evaluate concomitant medications that are likely to interact with the investigational drug in the clinical practice setting (e.g., add-on drug therapies or treatments for common co-morbidities) using a risk-based approach that considers the drug interaction mechanisms and the clinical significance of any changes in the drug's exposure. The relevant concomitant medications for study include those used to treat the same condition for which the investigational drug is being studied or those used to treat common co-morbidities in the patient population.

In Silico Studies

Physiologically based PK (PBPK) models can be used in lieu of some prospective DDI studies. Before using a PBPK modeling approach to predict the effects of moderate or weak perpetrator drugs on the exposure of an investigational drug, sponsors should verify the models using human PK data and information from DDI studies that used strong index perpetrators.

[3] FDA's Website on Drug Development and Drug Interactions can be found at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions.

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Background About the Guidance

DDIs are a significant but avoidable cause of morbidity and mortality associated with prescription drugs. The rate of adverse drug reactions increases significantly for patients who take four or more medications. Currently, close to 40 percent of the U.S. population receive prescriptions for four or more medications. FDA issued this guidance to provide best practices for clinical studies evaluating DDIs and recommendations for determining essential information to communicate in labeling to health care providers.

Drug Development Timeline – When to Apply the Guidance Recommendations?

During Clinical Development: After conducting in vitro drug metabolism and drug transporter studies, sponsors should determine the need for and timing of clinical DDI studies with respect to other studies in their clinical development program. Sponsors should assess the DDI potential before the product is administered to patients who are likely to take concomitant medications that could interact with the investigational drug. Furthermore, sponsors should collect enough DDI information to prevent patients from being unnecessarily excluded from any clinical study because of their concomitant medication use.

Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

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Speaker:
Dr. Kellie Reynolds, Director of the Division of Infectious Disease Pharmacology in the Office of Clinical Pharmacology

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Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about clinical drug interaction studies, read the guidance:

https://www.fda.gov/media/134581/download