In Vitro Drug Interaction Studies
Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions
Final Guidance for Industry

What is recommended in this guidance?
This final guidance provides recommendations for conducting and evaluating studies to determine the drug-drug interaction (DDI) potential of an investigational drug product. This guidance focuses on in vitro approaches to evaluate the interaction potential between investigational drugs with cytochrome P450 enzymes (CYPs) and transporters as well as how in vitro results can inform future clinical DDI studies.

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 outlines a general framework for conducting in vitro experiments and interpreting in vitro study results to determine the potential for clinical DDIs.

Why does the guidance focus on cytochrome P450 enzyme and transporter-mediated drug interactions?
CYP enzyme and transporter-mediated drug interactions are some of the most common mechanisms for affecting drug absorption, distribution, metabolism, and excretion (ADME) that can cause a DDI. Drug metabolism primarily occurs in the liver and intestine through the CYP family of enzymes. Membrane transporters can have clinically relevant effects on the pharmacokinetics and pharmacodynamics of a drug in various organs and tissues by affecting its absorption, distribution, and elimination.

In vitro evaluation of the DDI potential of an investigational new drug should involve the following:

1. Estimating the contribution of enzymes and transporters to the drug’s disposition
2. Characterizing the effect of the drug on enzymes and transporters
3. Informing the likelihood of clinical DDI as well as the need for clinical DDI studies

To learn more about in vitro cytochrome P450 enzyme and transporter-mediated drug interaction studies, read the guidance: https://www.fda.gov/media/134582/download
Taking more than one drug at the same time can alter the processes by which one or more of drugs is absorbed, distributed, metabolized, or excreted. This alteration is referred to as a drug interaction and can modify the drug's effectiveness or cause unexpected side effects. During drug development, it is not feasible to evaluate interaction with every potential coadministered drug in clinical trials. Therefore, evaluation often starts with in vitro experiments to identify mechanisms underlying potential DDIs. This guidance outlines a general framework for conducting in vitro experiments and interpreting in vitro study results to determine the potential for clinical DDIs.

Background About the Guidance

Starting in Preclinical Development and Through Clinical Development: Sponsors should conduct in vitro experiments to identify potential factors influencing drug disposition to elucidate potential DDI mechanisms and to yield kinetic parameters for use in further analyses. Results of in vitro experiments, along with clinical PK data and mechanistic modeling, can inform the need for and proper design of potential future clinical studies.

Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

Speaker:?
Dr. Xinning Yang, Policy Lead on the Guidance and Policy Team in the Office of Clinical Pharmacology

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about in vitro drug interaction studies, read the guidance: https://www.fda.gov/media/134582/download