

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.¹ 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.²



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

¹ For additional information, such as examples of substrates, inhibitors, and inducers of cytochrome P450 enzymes and transporters, please see the following website: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions>.

² If an in vitro assessment suggests a clinical DDI study should be conducted, sponsors should refer to the 2020 final FDA guidance for industry entitled *Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*.



Background About the Guidance

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.

Drug Development Timeline – When to Apply the Guidance Recommendations?



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 studies. 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.



PODCAST

Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

[CLICK HERE TO LISTEN](#)

Speaker:?

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

[CLICK HERE TO READ TRANSCRIPT](#)

To learn more about in vitro drug interaction studies, read the guidance: ?

<https://www.fda.gov/media/134582/download>