Expert Drug-Drug Interaction Study Design and Conduct

Patients are often prescribed multiple drugs concomitantly, which may increase the risk of drug-drug interaction (DDI) and potentially result in adverse effects or lead to reduced efficacy.

With more than half of marketed drugs being metabolized by cytochrome P450 enzymes (CYPs), inhibition or induction of CYP activity can greatly affect the absorption and metabolism of drugs. In addition, inhibition of drug transporter activity can also have an integral role in a drug's absorption, distribution and elimination. Therefore, understanding how an investigational drug interacts with CYP enzymes and drug transporters, either as a substrate or as a perpetrator (inhibitor/inducer), is important to assess during development.

A DDI study should also be considered if the study drug is anticipated to be co-administered with specific medications, such as combined oral contraceptives (COC) and acid-reducing agents (ARA):

- A DDI study with a COC may be warranted if the study drug is a CYP3A perpetrator and is intended for women 15-49 years of age (reflecting the age range women are typically on birth control pills).
- Changes in gastric acid pH can affect drug solubility and absorption, especially if physicochemical analysis suggests that the study drug is a weak-base or weak-acid. In this case, DDI investigation with an ARA (i.e. a proton pump inhibitor (PPI), histamine (H2) blocker, or antacid) may be recommended.

Celerion Differentiators:

Experience:

- Nearly 400 DDI studies since 2010
- 650 bed capacity accommodates multiple studies and parallel cohorts at once

Expertise:

- Dedicated expert team of Protocol Writers and PK Scientists
- Comprehensive list of validated bioanalytical drug assays

Efficiencies:

- Cocktail CYP and transporter approaches for substrate DDI studies
- Multi-part or adaptive study design to streamline protocol and start-up process
- Database of 48,500 healthy volunteers including pre- and post-menopausal women

Types of DDI Studies

Study Design Characteristics	Study Drug as a Substrate	Study Drug as Perpetrator	Study Drug Co-Administered with other Medications
Study Purpose	To examine the study drug exposure in response to inhibition or induction of CYPs and drug transporters	To determine the potential of the study drug to induce or inhibit CYP enzymes or drug transporters	**ARA:** • To assess the degree of pH-dependent interactions **COC:** • To determine the effect of the study drug on the efficacy and/or safety of COC
Study Design	Crossover (fixed-sequence or randomized) or parallel design if drug has a long half-life.		
Dose Regimen	IP as a substrate: • Single dose, unless auto-inhibition or auto-induction properties	• IP as an inhibitor: Single dose or multiple dosing if IP is a time-dependent inhibitor or if substrate has a long half-life • IP as an inducer: It may take 2 weeks of daily dosing of IP to achieve max level of induction	**ARA:** • Multiple doses of the IP is recommended if expected to affect the drug absorption **COC:** • Single dose or 1 cycle of COC with multiple dose IP

Types of DDI Studies (continued)

Study Design Characteristics	Study Drug as a Substrate	Study Drug as Perpetrator	Study Drug Co-Administered with other Medications
Participants	Healthy male and female participants		**ARA:** • Healthy males and females **COC:** • Healthy COC-naïve women, consider premenopausal females with multiple dosing for a PD effect
Sample size	Studies are typically not powered (n=16)		ARA: n=12-16 (not powered) COC: n=24-30
Key PK Parameters	AUC, C_{max}, T_{max}		

AUC, area-under-the curve; **C_{max}**, maximal concentration; **IP**, investigational product; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **T_{max}**, to maximal concentration

Bioanalytical Considerations:

Celerion offers a wide range of validated, bioanalytical drug assays for DDI studies developed with the smallest sample collection volume in mind and low levels of detection.

Available Common Bioanalytical Assays for DDI Studies

Substrates	Inhibitors/Inducers	ARA & COC
• Bupropion & hydroxybupropion • Caffeine & paraxantine • Dextromethrorphan & dextrorphan • Digoxin • Losartan & losartan acid metabolite • Midazolam & hydroxymidazolam • Omperazole & 5-OH omeprazole • R-warfarin, S-warfarin • Rosuvastatin	• Atorvastatin, parahydroxy-atorvastin & orthohydroxy-atorvastin • Clarithromycin & 14-hydroxy-clarithromycin • Clopidogrel & clopidogrel acid • Dabigatran (free & total) • Itraconazole & 7-OH-intraconazole • Phenytoin • Quinidine • Repaglinide	**ARA:** • Famotidine • Omperazole & 5-OH omeprazole **COC**: • Estradiol • Levonorgestrel; Ethinyl Estradiol • Norethindrone; Ethinyl Estradiol • Norgestrel (reported as Levonorgestrel)

View our full list of validated assays.