
Drug-Drug Interactions (DDI)

Cyprotex has extensive experience in DDI studies and is able to support full in vitro packages following US (FDA), European (EMA) and Japanese (PMDA) guidelines, as well as the new ICH M12 harmonised guidance. Initially, we work with you to design and plan your studies based on prior knowledge and data for your test article. Next, we implement the study in the laboratory according to the study design. Finally, we analyse, interpret and report on the data, and can assist with subsequent assessment of DDI risk.

▶ **Reaction Phenotyping**

- CYP and non-CYP enzymes
- microsomes with selective enzyme inhibitors or recombinant enzymes
- CYP % contribution using relative activity factors

▶ **Enzyme Inhibition**

- CYP and non-CYP enzymes
- reversible and time dependent

▶ **Enzyme Induction**

- fold change from mRNA and/or catalytic activity
- fold change, relative induction score and basic kinetic models

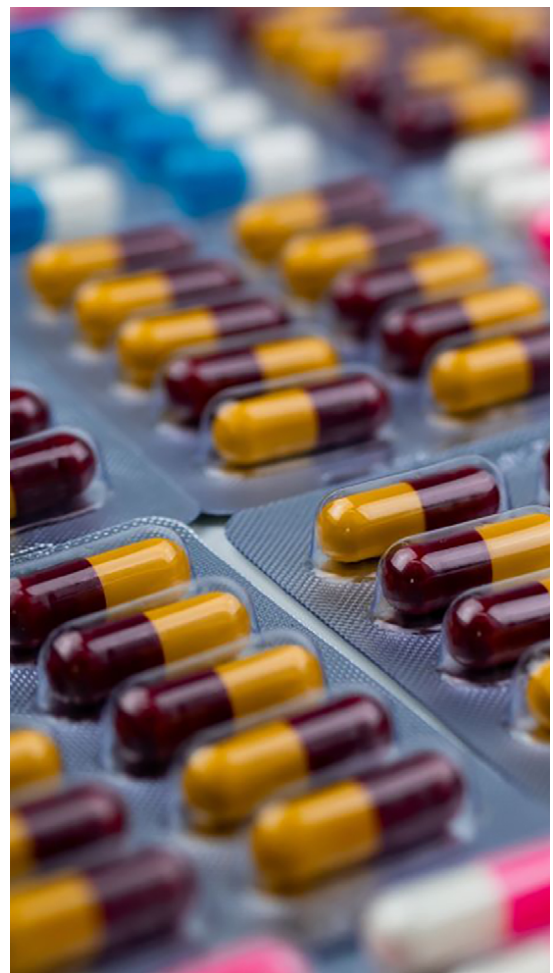
▶ **Transporter Substrate & Transporter Inhibition**

- full range of regulatory transporters plus additional non-regulatory transporters

▶ **Risk Assessment**

- regulatory DDI risk assessment
- quantitative (AUCR) prediction of statin DDIs

▶ **Supporting Assays for DDI Services**





Drug-Drug Interaction Services

- ▶ **From early stage screening to regulatory DDI packages.** We support you at all stages of the drug discovery and development continuum.
- ▶ **Perform the right assay at the right time.** We can guide you on the which assay to perform at each stage to reduce unnecessary expense.
- ▶ **Experienced consultants.** You have access to a DDI consultant who can support you with designing your study and can assist in assessing subsequent DDI risk.
- ▶ **Supporting services.** We offer a range of supporting services including solubility, plasma protein binding, microsomal binding, cytotoxicity, metabolite profiling and bioanalytical method development and feasibility.
- ▶ **Reports.** We have a full range of reporting options depending on your requirements from excel files to detailed written regulatory reports including eCTD-compliant reports.

Services & Capabilities

- ▶ Reaction phenotyping
- ▶ Enzyme inhibition
- ▶ Enzyme induction
- ▶ Transporter substrate ID
- ▶ Transporter inhibition
- ▶ Supporting ADME-Tox services

Experience

- ▶ Dedicated study managers are assigned to your project
- ▶ Consultancy from experienced DDI experts
- ▶ Full *in vitro* DDI packages following regulatory guidelines
- ▶ High quality data using validated methods
- ▶ Comprehensive range of supporting ADME-Tox services

Analytical Platforms

- ▶ LC-MS/MS, LC-MS
- ▶ High resolution mass spectrometry (HRMS)
- ▶ Radiochemical detection (³H and ¹⁴C)
- ▶ SelexION differential mobility separation
- ▶ Chromatography using different separation modes (HILIC, ion pair, ion exchange and chiral chromatography)

Selected Cyprotex DDI Publications

Mechanistic *in vitro* studies indicate that the clinical drug-drug interactions between protease inhibitors and rosuvastatin are driven by inhibition of intestinal BCRP and hepatic OATP1B1 with minimal contribution from OATP1B3, NTCP and OAT3.

<https://doi.org/10.1002/prp2.1060>

Studying the right transporter at the right time: an *in vitro* strategy for assessing drug-drug interaction risk during drug discovery and development. <https://doi.org/10.1080/17425255.2022.2132932>

Mechanistic *in vitro* studies indicate that the clinical drug-drug interaction between telithromycin and simvastatin acid is driven by time-dependent inhibition of CYP3A4 with minimal effect on OATP1B1. <https://doi.org/10.1124/dmd.118.083832>

Mechanistic *in vitro* studies confirm that inhibition of the renal apical efflux transporter multidrug and toxin extrusion (MATE) 1, and not altered absorption, underlies the increased metformin exposure observed in clinical interactions with cimetidine, trimethoprim or pyrimethamine. <https://doi.org/10.1002%2Fprp2.357>

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