CONCEPT LIFE SCIENCES

Cytochrome P450 (CYP) Induction Studies

De-Risking drug-drug interactions for regulatory success

Introduction

Interference between two drugs in the liver can alter the potency of the drugs and/or generate side effects. Cytochrome P450 enzymes are critical to the metabolic breakdown of many drugs and therefore, an important target for investigation. Providing evidence that there are no or limited drug-drug interactions (DDI) is crucial step in the development of safe and effective therapies and IND submissions

The Concept Life Sciences cytochrome P450 (CYP450) induction assay focuses on the most clinically relevant CYP450 enzymes. Cells, such as human hepatocytes, are cultured in the presence of candidate drugs and changes in enzymatic activity are determined by reverse transcription quantitative PCR (RT-qPCR) and liquid chromatography tandem mass spectrometry (LC-MS/MS).

The CYP450 induction assay supports compliance with FDA and EMA regulatory expectations whilst offering valuable mechanistic insights to strengthen regulatory submissions. By using clinically relevant human hepatocytes, our assays enable accurate prediction of DDI risk and provide flexibility through early-phase screening or comprehensive full-panel formats suitable for both early and late-stage programs. With optional GLP-compliant workflows, our services help de-risk development programs, facilitate confident decision-making, and are particularly suited for clients in preclinical or IND-enabling stages preparing submissions to global regulatory authorities.

Methods

Cryopreserved hepatocytes are thawed and cultured for 48-72 hours in the presence or absence of test compounds and media is refreshed daily (Figure 1). Our team focuses on the most clinically relevant CYP450 enzymes - CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4. Changes in the level of metabolites in the presence of different probe substrates are quantified at gene and enzyme activity levels to provide a comprehensive view of metabolic response (see Table 1). Enzyme activity, mRNA levels, cytotoxicity and protein are expression are quantified to provide a full picture of induction potential.

CYP Isoform	Probe Substrate	Analyte (Metabolite)
CYP1A2	Phenacetin	Acetaminophen
CYP2B6	Bupropion	Hydroxybupropion
CYP3A4	Midazolam	1-Hydroxymidazolam
CYP2C8	Amodiaquine	N-Desethylamodiaquine
CYP2C9	Diclofenac	4-Hydroxydiclofenac
CYP2C19	S-Mephenytoin	4-Hydroxymephenytoin

Table 1: Substrates and analytes for catalytic activity

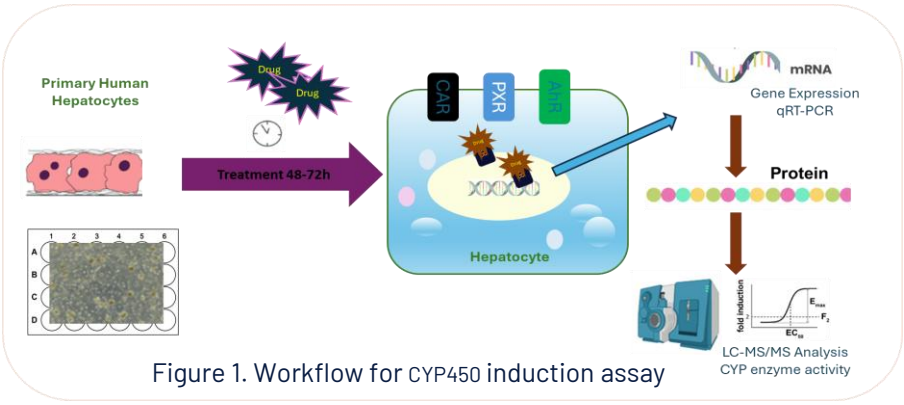

Figure 1. Workflow for CYP450 induction assay

Assay selection

Preliminary validation of test item solubility and cytotoxicity assessment is recommended. Test items can then be screened using a restricted CYP panel and pooled human hepatocytes to derisk moving to a full CYP screening panel (see below).

Service Tier	CYPs Assessed	Test System	Application
Screening Panel	CYP1A2, CYP2B6, CYP3A4	Pooled Human hepatocytes; 48h treatment	Early decision-making
Full Panel	+ CYP2C8, CYP2C9, CYP2C19	3 Human donors (hepatocytes; 72h treatment	Regulatory and late-stage

Table 2: CYP Induction Panel

Endpoint measures include mRNA expression (RT-qPCR) and catalytic activity (LC-MS/MS). A full data report and report are provided with screening and full panel assays.

Data analysis and results

Data are evaluated against vehicle and reference inducers (see Table 2). Results include fold induction vs. control, Emax/EC50 calculations (4-parameter nonlinear fit), and statistical normalization across donors.

CYP Isoform	Nuclear Receptor	Positive Control
CYP1A2	Ahr	Omeprazole
CYP2B6	CAR	Phenobarbital
CYP3A4 CYP2C8 CYP2C9 CYP2C19	PXR	Rifampicin
Negative Control: Flumazenil		

Table 2: Positive Controls for CYP Isoforms

Data output

- Fold induction vs. vehicle control
- Emax, EC50 (4-parametric nonlinear fit, if applicable)
- Raw and summary Excel data
- Optional full written report.

Conclusions

These insights help de-risk your development program and support confident decision-making as you move your compounds forward. Our CYP induction studies provide critical insights into metabolic interactions, helping you:

- Identify and mitigate DDI risks early
- Streamline regulatory submissions
- Advance compounds with confidence

Partner with Concept Life Sciences to navigate the complexities of CYP induction with clarity, precision, and scientific integrity.

- ✓ GLP-compliant workflow on request
- ✓ Target clients in preclinical or IND-enabling stages, especially those submitting to regulators

Key Features

- Identify and mitigate drug-drug interactions
- Supports compliance with FDA and EMA regulatory expectations
- Utilises clinically relevant human hepatocytes and CYP450 enzymes
- Cascade of assays to derisk test item progression