# CYP450 Induction Services

At BioIVT, we recommend implementing CYP induction studies using TRANSPORTER CERTIFIED™ hepatocytes in sandwich culture. We have demonstrated that this model can show better IVIVE correlations vs. conventional, transporter-deficient models because it incorporates biliary efflux whereas conventional models do not. In comparison, to conventional systems the model better maintains physiologically-relevant intracellular concentrations of drug candidates, which is critical for preventing cytotoxicity at higher concentrations suggested by the FDA. The latest FDA Guidance (*In Vitro* Drug Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies, 2017) recommends testing compounds to the limit of solubility or until cytotoxicity is observed. If efflux transporter function is deficient, compounds can accumulate in hepatocytes and cause toxicity. If the hepatocytes have complete transporter function and are able to clear the compound as *in vivo*, higher concentrations of compound may be tested.

## CYP Enzyme Induction Services

Our support for CYP450 research includes the following programs:

- Screening Assays: Used for lead selection and early determination of DDI potential.
- Regulatory Submission Package: Assay programs that meet FDA and EMA requirements for a regulatory submission.
- Customized Research Programs: Studies designed to address clients' specific needs

| PARAMETER | SCREENING ASSAY | REGULATORY SUBMISSION PACKAGE |
|---|---|---|
| Model | TRANSPORTER CERTIFIED human hepatocytes in sandwich culture | TRANSPORTER CERTIFIED human hepatocytes in sandwich culture |
| Test Article Concentrations | 3 | 3 or 7* |
| Donors | 1 | 3 |
| CYP Enzyme with Positive Controls | 1A2 (omeprazole), 2B6 (phenobarbital) 3A4 (rifampicin) | 1A2 (omeprazole), 2B6 (phenobarbital)** 3A4 (rifampicin) |
| Nuclear Receptor Pathways representing | AhR, CAR, PXR | AhR, CAR, PXR |
| Exposure period | 72 hours | 72 hours |
| Output | Positive vs. No Response | $EC_{50}$ and $E_{max}$ (per FDA guidelines) |
| Deliverables | Data and summary tables | eCTD-compliant report including data, summary tables, description of materials and methods, and analyses |

*3 concentrations recommended if induction is not expected based on other evidence.
7 concentrations is recommended if induction is expected.
**EMA recommends 0.1 µM CITCO

## TRANSPORTER CERTIFIED Hepatocytes

TRANSPORTER CERTIFIED hepatocytes is an industry standard that ensures the hepatocytes have transporter function and are metabolically competent and have appropriate gene regulation pathways. In sandwich culture, the intracellular concentrations in TRANSPORTER CERTIFIED hepatocytes reflect physiologic conditions because the hepatocytes express functioning uptake and efflux transporters and develop bile pockets similar to bile canaliculi.

## Cytochrome P450 Induction Assays

CYP450 induction assays evaluate the potential of a compound to upregulate metabolic pathways. A compound that induces CYP450 enzymes may alter the metabolism of other drugs, resulting in the loss of the drug's efficacy. Evaluating the drug-drug interaction (DDI) potential of a new chemical entity is critical to the candidate selection, clinical development, and ultimately the regulatory approval process. Stakeholders within the industry, academia, and regulatory bodies accept sandwich-cultured human hepatocytes as an appropriate *in vitro* model to assess the potential for drug candidates to induce human CYP450 expression.

## How Clients Use Our CYP Induction Model

Our clients rely on our induction study data to guide decision-making throughout their drug discovery and development programs:

- Lead selection
- Clinical study design, relating to DDI concerns
- Regulatory submissions
- Response to regulators' questions

Improved *in vivo* relevance (ICC, Toxicity, Induction, DDIs)

| TRANSPORTER DEFICIENT MODEL | TRANSPORTER CERTIFIED™ HEPATOCYTE MODEL |
|---|---|
| **RISKS:** | **BENEFITS:** |
| • False positives require additional DDI studies :<br>  • Increase cost<br>  • Lengthen timeline<br>• Failure to select optimal leads | • Reduce risk of false positives<br>• Inform clinical development strategy<br>• Support regulatory submissions |

## See How We've Helped Others:

### CASE STUDY: OBETICHOLIC ACID CYTOTOXICITY & CYP450 INDUCTION POTENTIAL

**Situation:** Intercept Pharmaceuticals Inc. had conducted hepatotoxicity and CYP induction studies for obeticholic acid (OCA) using a transporter-deficient model. The model predicted much higher toxicity and a far greater impact on CYP expression than what was observed in *in vivo* models.

**Problem:** The monolayer, transporter-deficient model could not account for biliary efflux, resulting in over-predicting toxicity and DDI potential. The model data did not correlate with clinical data.

**Our Solution:** We conducted an *in vitro* study using human TRANSPORTER CERTIFIED hepatocytes in sandwich culture.

**Results:** The toxicity and DDI predictions from our model were well-correlated with clinical DDI study data. Intercept included our data in subsequent regulatory submissions. The FDA approved Ocaliva® (obeticholic acid) in May 2016, indicated for primary biliary cholangitis.

The BioIVT model correctly predicted clinical results because it incorporates efflux transporter function, resulting in a physiologically-relevant ICC, whereas the conventional transporter-deficient model did not.

| CYP450 Isoforms | Conventional Model Prediction | QTS Model Prediction | Clinical Observation |
|---|---|---|---|
| 1A2 | Significant Suppression | Minimal Suppression | Minimal Increase |
| 2B6 | Significant Suppression | Minimal Suppression | Not Evaluated |
| 3A4 | Significant Suppression | Minimal Suppression | No Effect |
| 2D6 | Not Evaluated | No Effect | No Effect |
| 2C9 | Not Evaluated | No Effect | No Effect |
| 2C19 | Not Evaluated | No Effect | Minimal Suppression |
| BCRP<br>OATP 1B1<br>OATP 1B3 | Not Evaluated | Minimal Suppression | Minimal Increase |

## Collaborating with BioIVT

BioIVT takes a collaborative approach in all our projects. Your project will be assigned to a study team with extensive experience in designing, implementing, and interpreting the results from induction studies. We are familiar with both FDA and EMA guidance documents and we provide consulting support to ensure that study results can be used for regulatory submissions and meet the needs of your internal and external stakeholders. We view our clients as partners and have structured our processes to be flexible and adaptable to meet changing project requirements, and at the same time ensure that we provide high-quality deliverables on-time and within budget.


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