BIOIVT
ELEVATING SCIENCE®

Metabolism Studies

Trusted Partner for Hepatic Products and Research Services

Drug metabolism studies play a key role in identifying new chemical entities with optimal pharmacokinetic properties. BioIVT offers a comprehensive portfolio of hepatic products for *in vitro* metabolism studies. Our research services group designs and implements preclinical programs to help our clients achieve their research objectives.

Innovative Tools for Metabolism Studies

We have earned a reputation for excellence by having the highest quality standards, ethical procurement of tissues, largest lots in the industry and extensive inventory options and choices. Additionally, we offer unique products including HEPATOPAC® kits for long-term stable hepatocyte cultures and LIVERPOOL® hepatocytes, providing the benefits of large pooled lots.

Leading Hepatic Products to Support Your Programs	
HEPATOPAC Kits	Animal Subcellular Fractions
INVITROCYP™ Microsomes	Fresh, Cryosuspension. and Cryoplateable Hepatocytes
LIVERPOOL Hepatocytes	INVITROGRO™ Media

Hepatic products available for human and animal models.

HEPATOPAC Technology

HEPATOPAC Technology is used to create stable hepatocyte cultures that enable long-term metabolism and toxicity studies.

Compared to conventional systems, the HEPATOPAC model has demonstrated improved IVIVC in detecting primary and secondary excretory metabolites and can be used to stratify low turnover compounds in a chemical series. Additionally, the HEPATOPAC model demonstrates species-specific metabolism recapitulating in vivo metabolic profiles and enables adherence to the 2016 FDA Guidance for Industry, "Safety Testing of Drug Metabolites".

- *Long-term stability and functionality (~ four weeks)*
- *Primary hepatocytes that are extensively characterized and validated*
- *Multi-species platform (Human, Rat, Dog and Monkey)*
- *High-throughput format*

See How We Helped Others

Loratidine (LOR, Claritin) and its metabolite desloratidine (DL, Clarinex) are antihistamines, approved in 1993 and 2001 respectively, to treat allergic rhinitis. The major human circulating and urinary metabolite of LOR, 3-OH-DL glucuronide was not detected in microsomes, S9 or hepatocyte suspensions. Furthermore, this metabolite was not generated in appreciable amounts during preclinical safety studies in mice, rats and monkeys - a concern during the FDA approval process. However, 3-OH-DL glucuronide was detected in human HEPATOPAC cultures. The success of the HEPATOPAC model in generating *in vivo* relevant metabolites can help minimize drug candidate failures and delays in bringing new drugs to patients. (Aratyn-Schaus Y. *et. al.* 2016, Bioanalysis)

Metabolism Research Studies

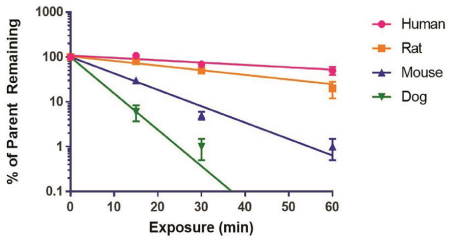
Either as stand-alone studies, or as part of a comprehensive ADME-Tox program, we conduct *in vitro* evaluations of metabolism including the following studies:

- Metabolite Identification
- Metabolic Stability
- Reaction Phenotyping

In Vitro Models for Metabolism	Metabolite Identification	Metabolic Stability	Reaction Phenotyping
Microsomes		✓	✓
Suspension Hepatocytes	✓	✓	
HEPATOPAC® Culture	✓	✓	

Our team partners with you to select the appropriate model for metabolism studies. During the design process for your metabolism study program, we provide recommendations based on the characteristics of the compound and your research objectives. Our investigations of metabolism help our clients understand the hepatobiliary disposition, toxicological properties and Drug-Drug Interaction (DDI) potential of parent compounds and metabolites. We provide submission-ready data and reports because our methods comply with regulatory guidelines including the FDA Draft Guidance published in 2017, '*In Vitro* Drug Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies'.

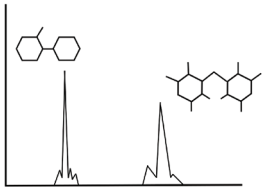
Metabolic Stability Assays



The ideal model may depend on rate of compound clearance and mechanism of metabolism.

- **Microsomes:** High uptake and clearance compounds likely metabolized by CYPs.
- **Suspension Hepatocytes:** High uptake and clearance compounds metabolized by phase 1 and phase 2 enzymes.
- **HEPATOPAC Cultures:** Low clearance and highly stable compounds requiring long-term studies. Additionally, HEPATOPAC cultures are amendable to high-throughput assay formats. Multi-species comparisons can be made in each model.

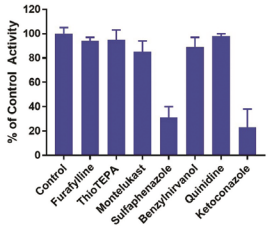
Metabolite Identification Assays



The ideal model may depend on rate of compound clearance and mechanism of metabolism.

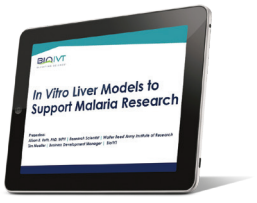
- **Suspension Hepatocytes:** High uptake and clearance compounds. We typically include the time points: 0, 15, 30, 60, 120 and 240 minutes.
- **HEPATOPAC Cultures:** Low clearance compounds that may be slowly metabolized.

Reaction Phenotyping Assays



We implement reaction phenotyping studies with microsomes to identify the CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5) that may be involved in the metabolism of the parent compound. Our typical studies include correlation analysis, K_m value determination, recombinant human CYPs activity and inhibition.

For Additional Resources Visit BioIVT.com



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