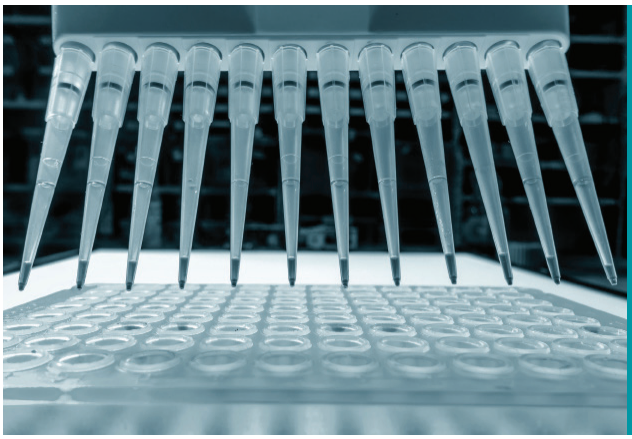
BIOIVT
ELEVATING SCIENCE®

Hepatic Disposition Studies



Select and Develop Leads with Favorable Pharmacokinetic Profiles

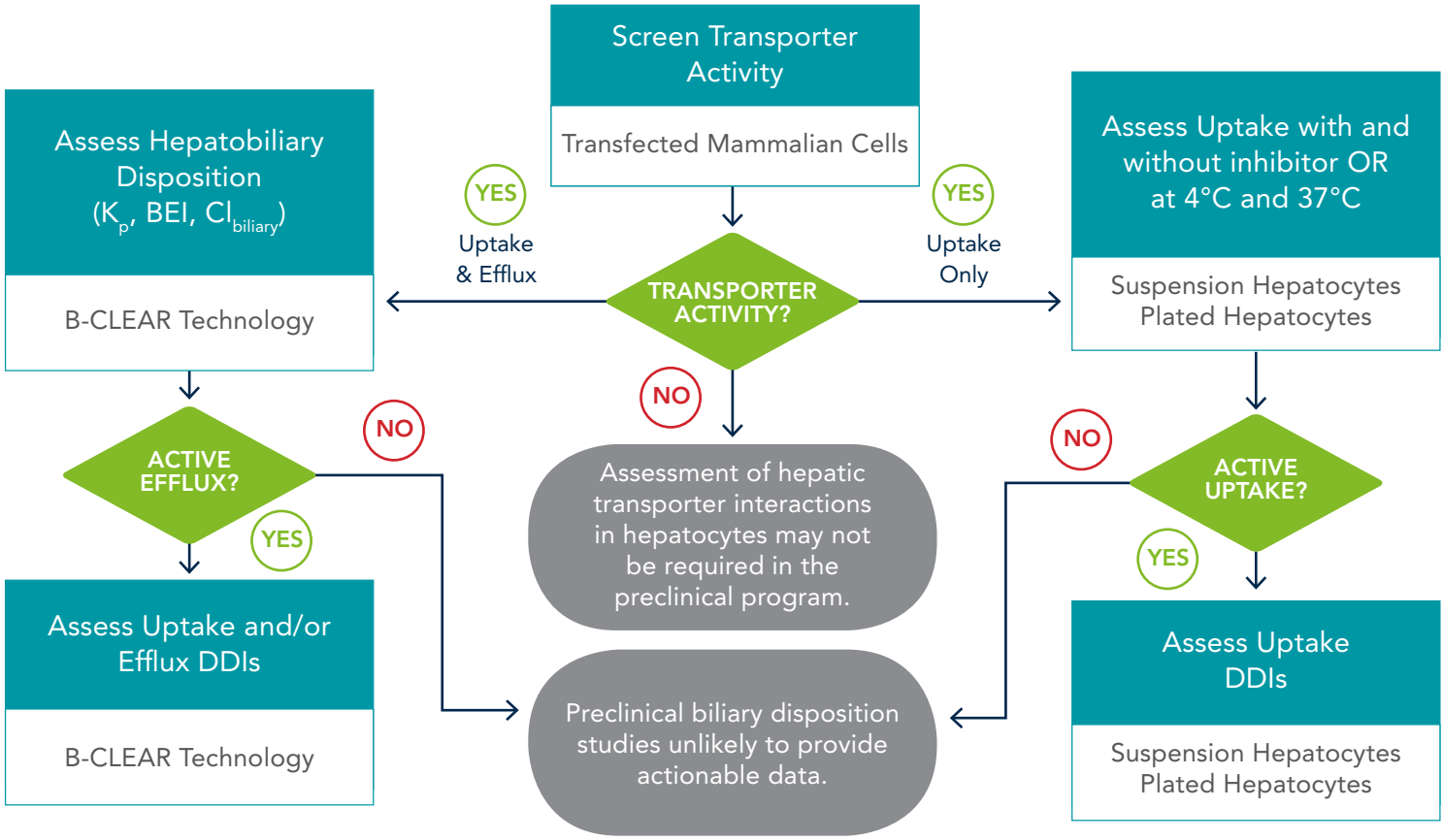
At BioIVT, we provide leading expertise to design and implement *in vitro* hepatic disposition studies to inform lead selection and optimization decisions, answer mechanistic questions and address regulatory concerns. Whether hepatic disposition studies are conducted as comprehensive programs or as stand-alone studies, our objective is always to help our clients achieve their R&D goals.

Comprehensive Research Programs

Assessing hepatic uptake, accumulation and disposition is critical for predicting the pharmacokinetics of a compound, designing ADME-Tox programs and in interpreting data from preclinical studies. We recommend that hepatic disposition programs start with a screening study to determine if a compound inhibits or is a substrate for uptake and efflux transporters. Following the transporter screening assessment, hepatic accumulation, disposition and DDIs may be assessed using one of the following methods:

- B-CLEAR® Technology for compounds that show transporter-mediated uptake and efflux, or just efflux
- Suspension or plated hepatocytes for compounds that show only transporter-mediated uptake

In Vitro Hepatic Disposition Assessment Program



Service offerings and Products

Transporter Screening

We evaluate uptake and efflux transporters that are known to be important in the pharmacokinetics of many drugs. We offer over 100 single-transporter assays and multi-transporter models and can customize the transporter screening program based on your requirements. Typically, we use our OPTI-REGULATORY™ panel, a selection of transporters that regulatory agencies recommend be evaluated as part of IND submissions.

Do It Yourself

Conduct transporter studies with our ready-to-use TRANSFLEX™ Plates

B-CLEAR Technology

Our novel "parallel-well design" method using B-CLEAR® Technology enables us to quantitate biliary vs. basolateral efflux and so provide an *in vivo*-relevant estimate of hepatic disposition. As part of B-CLEAR studies, we calculate hepatic accumulation (K_p), intracellular concentration, the biliary excretion index (BEI), biliary clearance ($Cl_{biliary}$) and investigate the potential for disposition DDIs. Data can be used to select analogs with the optimum clearance properties and assess the relevance of *in vivo* clearance models.

Do It Yourself

Implement B-CLEAR studies with our ACCULIVER® Biliary Clearance Kits

Suspension and 3-Hour Plated Methods

Using the suspension or 3-hour plated hepatocytes, we estimate transporter-mediated uptake, uptake rate if multiple timepoints are included, uptake clearance (Cl_{uptake}) and hepatic accumulation (K_p). We recommend these methods if screening studies show that there is minimal transporter-mediated efflux. Both studies may be designed with multiple timepoints and are done either with and without an inhibitor or at 4°C and 37°C to evaluate active vs. passive uptake. After incubations, we separate hepatocytes from free drug using the oil spin suspension assay. The suspension method can be implemented using rat, dog, monkey or human hepatocytes and allows for species comparison studies.

Do It Yourself

Extensive portfolio of hepatocyte products

See How We've Helped Others:

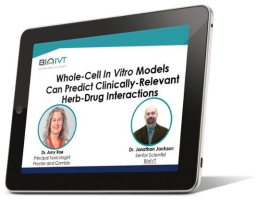
Evaluation of ERAs as Hepatobiliary Transporter Inhibitors

Gilead Sciences, Inc., was developing endothelin receptor antagonists (ERAs) as therapies for pulmonary arterial hypertension. ERAs were thought to have a risk of hepatotoxicity, likely due to inhibition of hepatic uptake or efflux transporters. Using B-CLEAR® Technology, we evaluated ERA hepatic transporter interactions and addressed specific questions from the FDA. We compared Gilead's analogs to other ERAs including bosentan and sitaxsentan. Our study design included both rat and human hepatocytes, allowing for a species comparison. The data showed that Gilead's compounds in development had less human transporter interactions and improved hepatobiliary disposition relative to the comparators. Gilead included our data in their regulatory submission, helping them to advance their product development program.

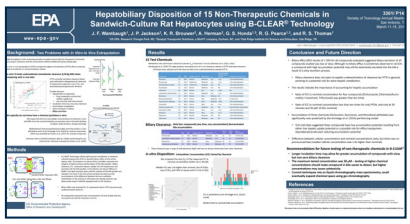
We collaborated with Gilead to publish the study results (*Lepist E. et. al. (2014) PLOS ONE, 9(1), 1–10 https://doi.org/10.1371/journal.pone.0087548*).

For Additional Resources, Visit BioIVT.com

Webinars



Posters



Insights from Our Experts

MEET THE BIOIVT EXPERTS

BioIVT.com

For Inquiries:

North America & Asia Pacific
T +1 516 483 1196 **F** +1 516 483 4683
E customerservice@bioivt.com

Europe, Middle East & Africa
T +44 (0) 1444 250010 **F** +44 (0) 1444 250066
E cseurope@bioivt.com

© 2019 BioIVT. BIOIVT, ELEVATING SCIENCE, B-CLEAR, OPTI-REGULATORY, TRANSFLEX and ACCULIVER are trademarks and registered trademarks of BioIVT, LLC.