SEKISUI XENOTECH

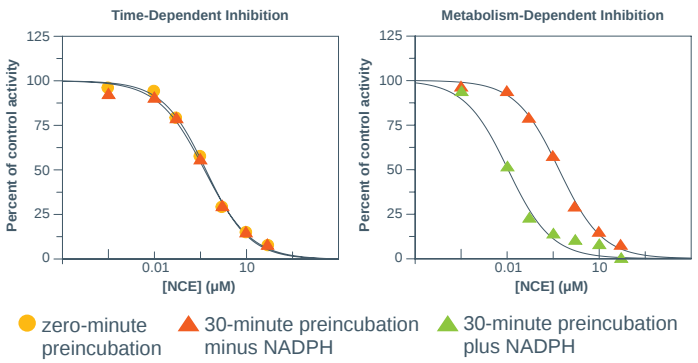
Sekisui XenoTech designs studies to evaluate CYP inhibition by drug candidates and/or their potential metabolites.

Clinically significant CYP inhibition can be caused by a drug candidate or by one of its metabolites, as was the case with Posicor® (mibefradil), which was withdrawn from the US market after it was discovered to be a metabolism-dependent inhibitor (MDI) of CYP3A4. Sekisui XenoTech is well-equipped to calculate the FDA/EMA R_1 values for direct inhibition and R_2 values for time-dependent inhibition.

Our efficient 3-curve IC_{50} study design allows us to evaluate CYP enzyme inhibition by drug candidates and their potential metabolites, predicting potential clinical issues in the *in vitro* development phase. Sekisui XenoTech's CYP inhibition assays are performed with an extensively-characterized lot of pooled human liver microsomes to assure consistency throughout every study. Automated data acquisition, retrieval and processing capabilities coupled with robotics and a LIMS assures fast turnaround times and publication quality reports.

We address many scientific concerns when designing our studies to provide high content, high quality data. Low protein concentration and a short marker substrate incubation time minimizes artifacts caused by protein binding, metabolic instability of the test article and excessive metabolism of the marker substrate. Our follow-up studies support the further characterization of drug candidates that are identified as potent direct or metabolism-dependent inhibitors (for example: K_i determinations, XTRA: XenoTech Reversibility Assay and K_I / k_{inact} determinations). This mechanistic information can help you to better understand the potential for clinical issues at this early stage of compound development. Regulatory agencies suggest doing a k_{inact} study if MDI is detected, however if the MDI is reversible, initiating a k_{inact} study would provide no benefit to the customer.

3-curve IC_{50} data predicts CYP inhibition by the test article and by its potential metabolites



Validated LC-MS/MS Methods with commonly used probe substrates feature deuterated internal standards to minimize test article interference.

CYP	Reaction
1A2	Phenacetin *O*-dealkylation
2A6	Coumarin 7-hydroxylation
2B6	Efavirenz 8-hydroxylation
2B6	Bupropion hydroxylation
2C8	Amodiaquine *N*-dealkylation
2C8	Paclitaxel 6α-hydroxylation
2C9	Diclofenac 4´-hydroxylation
2C19	*S*-Mephenytoin 4´-hydroxylation
2D6	Dextromethorphan *O*-demethylation
2E1	Chlorzoxazone 6-hydroxylation
3A4/5	Midazolam 1´-hydroxylation
3A4/5	Nifedipine oxidation
3A4/5	Atorvastatin *o*-hydroxylation
3A4/5	Testosterone 6β-hydroxylation

Sekisui XenoTech CYP Inhibition Study Features:

- Robotic incubations
- Efficient 3-curve IC_{50} study design calculated from several concentrations of the drug candidate
- Validated methods with commonly used probe substrates
- Direct and time-dependent positive controls included
- Optional follow-up mechanistic studies
- Automated data retrieval and data processing
- CFR 58, Part 11 compliant systems
- Available as GLP or non-GLP

Sekisui XenoTech CYP Inhibition Study Benefits:

- High-content evaluation of inhibition potential
- Predict clinical outcomes with greater confidence
- Full compliance with all regulatory agencies
- Fast turnaround time
- Publication-quality reports
- Consultative interpretation of results

Contact us to learn more at **www.xenotech.com** or call **913.438.7450**.

A Typical CYP Inhibition Study Decision Tree