

CYP INHIBITION SERVICE WITH RAPIDFIRE®

High throughput CYP Inhibition service with FDA-recommended probe substrates

Inhibition of cytochrome P450 enzyme catalytic activity is a leading mechanism of metabolism-based drug-drug interactions. In vitro inhibition studies are valuable predictors of in vivo drug-drug interactions and the magnitude of that interaction. In many cases, this information can eliminate the need for further in vivo studies. The in vitro ADME market leader in P450 products and services, BD Biosciences, and the technology leader in high-throughput mass spectrometry, BIOCIUS Life Sciences, are combining expertise to provide a novel mass spectrometry-based, high-throughput complete service package for cytochrome P450 inhibition. BD Biosciences' validated assay methods combined with BIOCIUS's RapidFire® high-throughput mass spectrometry technology provide researchers a high-quality, cost-effective inhibition screening service. Only BD GentestSM Contract Research Services delivers a combination of industry leading proprietary products, advanced technology, expert guidance from renowned study directors and reliable, submission ready results. Together, these elements provide you with the most rapid path to more sound decision making in your drug discovery endeavors.

The **most rapid** path to more sound decision making.

HIGH-QUALITY MASS SPECTROMETRY DATA

GLP-validated assay methods are used in a high throughput mode using BIOCIUS's RapidFire® mass spectrometry technology and BD UltraPool™ HLM 150 large donor pool. Cytochrome P450 inhibition IC₅₀ results obtained using RapidFire analysis were comparable to those obtained using validated traditional LC/MS/MS methods (>90% of values are within 2-fold of each other). The combination of robust multi-point assays, FDA recommended drug probes individual incubations, and use of stable-labeled isotopes provides a high-quality rapid CYP inhibition screening assay.

TIME-DEPENDENT INHIBITION USING UNIQUE TWO-TIME POINT IC₅₀ SHIFT ASSAY ELIMINATES TRIAL AND ERROR

BD Biosciences time-dependent inhibition service uses a unique, two-time point IC₅₀ shift assay designed to save time^[1]. This newly developed validated method simplifies preincubation time point selection, eliminating trial and error associated with K_i/k_{inact} experimental design. The USFDA draft guidance on drug interactions (Sept, 2006^[2]) advocates testing for time-dependent inhibition.

[More on reverse](#)

KEY FEATURES

Delivers Rapid Turnaround of Data

- Sponsors provide investigational drugs and BD provides the full solution
- Conventional LC/MS/MS quality data in a fraction of the time
- One-week turn around

Provides High-Quality Data Analysis

- FDA-recommended drug probes individually incubated and analyzed
- Uses BD UltraPool™ HLM 150 liver microsomes to provide lot-to-lot consistency
- Full 7-point IC₅₀ curves rather than single concentration inhibition data
- Mass spectrometry data with stable-labeled isotopes to control for test-article induced ion suppression

Time Savings

- Complete package of sample preparation and data analysis

bdbiosciences.com

To inquire about BD GentestSM Contract Research Services,

contact 888.334.5229 x2246 or 781.935.5115 x2246.

Outside the U.S., visit bdbiosciences.com/offices to locate your nearest BD Biosciences office.



CYP INHIBITION SERVICE WITH RAPIDFIRE®

SPECIFICATIONS:

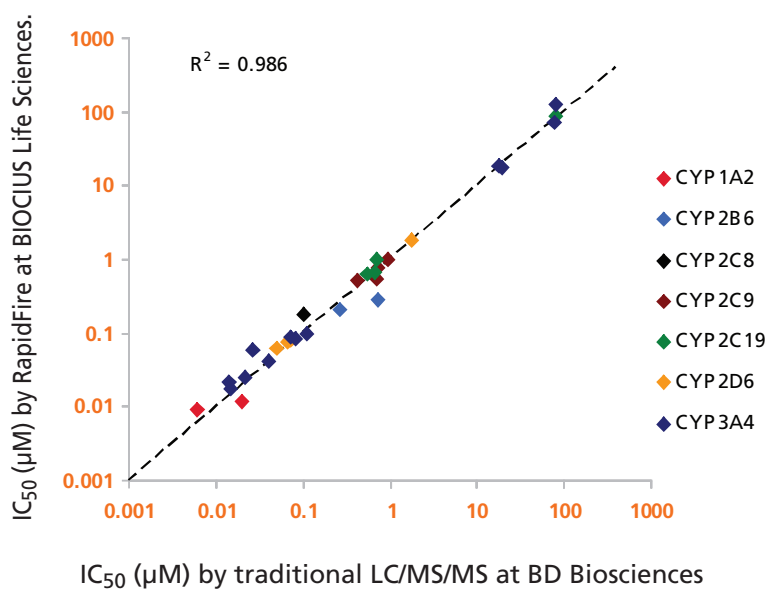
STUDY DESIGN SUMMARY

TEST SYSTEM:	Pooled Human Liver Microsomes (HLM), BD UltraPool™ HLM 150.
CONCENTRATIONS:	7, singlicate.
ASSAY METHOD:	Test article is incubated with pooled human liver microsomes, an NADPH-regenerating system, and current FDA recommended drug probe substrates.
RECOMMENDED PROFILE:	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4.
ANALYTICAL METHOD:	RapidFire mass spectrometry.
REPORT:	IC ₅₀ Values. Percent inhibition at each concentration of the test article. Excel-based data report.

CYP ASSAYS AND SUBSTRATES

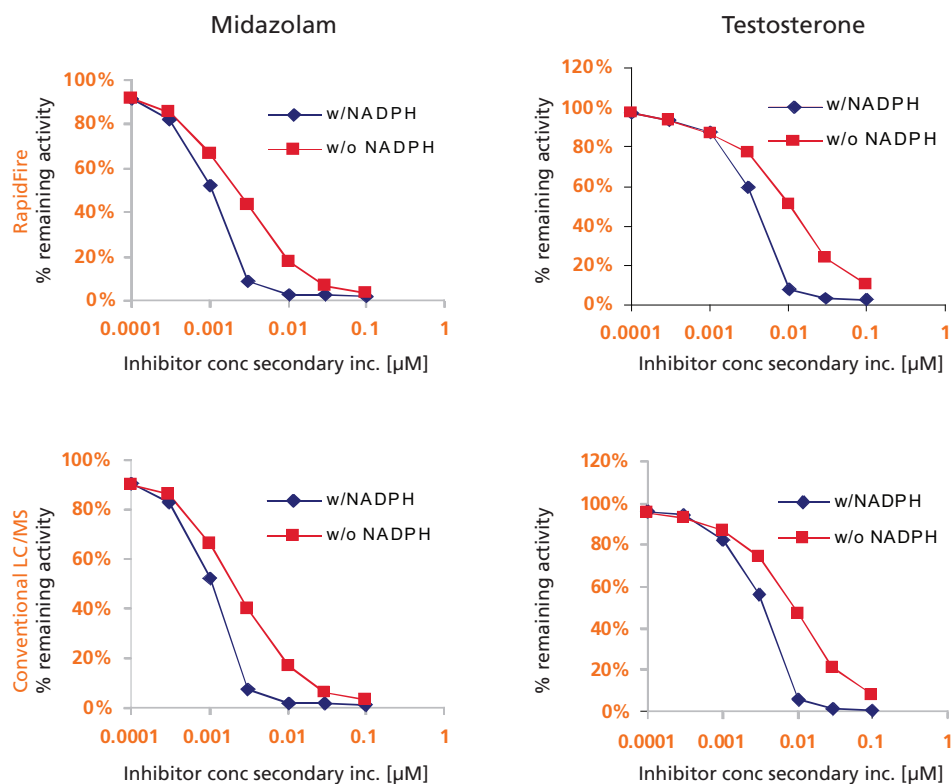
P450 Enzyme	Probe Substrate
CYP1A2	Tacrine
CYP2B6	Bupropion
CYP2C8	Amodiaquine
CYP2C9	Diclofenac
CYP2C19	S-mephenytoin
CYP2D6	Dextromethorphan
CYP3A4	Midazolam, Testosterone

CORRELATION DATA BETWEEN CONVENTIONAL LC/MS AT BD BIOSCIENCES AND RAPIDFIRE® AT BIOCIUS LIFE SCIENCES



Data from 8 different enzyme/substrate pairs and 1 to 3 inhibitors for each pair was generated using traditional LC/MS/MS at BD Biosciences and RapidFire® technology at BIOCIUS Life Sciences. Inhibitors include ketoconazole, α -naphthoflavone, montelukast, S-benzylrivanol, sulfaphenazole, azamulin, paroxetine, ticlopidine, S-fluoxetine, tienilic acid, verapamil, and diltiazem.

RITONAVIR IC₅₀ SHIFT WITH MIDAZOLAM AND TESTOSTERONE USING RAPIDFIRE® ANALYSIS



	Midazolam	Testosterone
Conventional LC/MS/MS	Preincubation w/ NADPH = 11 nM Preincubation w/o NADPH = 22 nM Shift = 2.04	Preincubation w/ NADPH = 3.9 nM Preincubation w/o NADPH = 9.4 nM Shift = 2.40
RapidFire Analysis	Preincubation w/ NADPH = 11 nM Preincubation w/o NADPH = 24 nM Shift = 2.17	IC ₅₀ Preincubation w/ NADPH = 4.4 nM IC ₅₀ Preincubation w/o NADPH = 11 nM Shift = 2.47

References

- [1] Perloff ES, Andrew K. Mason, Shangara S. Dehal, Andrew P. Blanchard, Ling Morgan, Thuy Ho, Andre Dandeneau, Ronell M. Crocker, Catherine M. Chandler, Nathalie Boily, Charles L. Crespi, and David M. Stresser (2009) Validation Of Cytochrome P450 Time Dependent Inhibition Assay: A Two Time Point IC₅₀ Shift Approach Facilitates Kinact Assay Design. *Xenobiotica* 39:99-112.
- [2] FDA Draft Guidance for Industry - Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (September 2006).