



## METABOLIC STABILITY IN MICROSOMES

### Assays performed in human and animal microsomes to predict the intrinsic clearance or metabolic half life of a test article

High throughput metabolic stability assays using liver microsomes from human and pre-clinical species provide a rapid understanding of in vitro metabolic pathways of a test article and its potential for drug-drug interactions. This rapid assessment of a test article's half-life is a good indicator of in vivo clearance thus facilitating decisions for follow up in vivo testing and the design of clinical trials. Only BD Gentest<sup>SM</sup> 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.

#### FULLY CHARACTERIZED LARGE HUMAN DONOR POOL MINIMIZES VARIABILITY BETWEEN DONORS AND PROVIDES CONSISTENT DATA FROM ASSAY TO ASSAY

BD utilizes its BD UltraPool<sup>TM</sup> HLM 150 donor pool consisting of 150 donors statistically modeled so that lot-to-lot variability represented as coefficient of variation (CV) is <10% (mean) for the more variable CYP enzyme (CYP2C19), and <5% (mean) for the key drug metabolizing CYPs (CYP1A2, CYP2C9, CYP2D6 and CYP3A4).

#### COMPARISON OF MICROSOMAL METABOLIC STABILITY ACROSS SPECIES

Metabolic stability determinations can be performed using a variety of subcellular fractions (microsomes, S9, cytosol) from human and animal liver (mouse, rat, dog, guinea pig, rabbit, mini-pig, and cynomolgus monkey, and others) as the enzyme source, allowing inter-species comparisons.

#### ACCURATE AND REPRODUCIBLE RESULTS

Results obtained at BD Biosciences using BD Gentest<sup>TM</sup> human and animal liver microsomes are consistent with data reported in the literature. Results are highly reproducible over extended periods of time using various lots of microsomes.

[More on reverse](#)

#### KEY FEATURES

- Maintains data consistency from assay-to-assay with a mixed gender human liver microsomes donor pool consisting of 150 donors
- Available using a variety of subcellular fractions (microsomes, S9, cytosol) from human and animal liver (mouse, rat, dog, guinea pig, mini-pig, rabbit, cynomolgus monkey) as the enzyme source
- Provides  $t_{1/2}$  and  $CL_{int}$  data consistent with the reported literature
- Uses 0.5 - 1.0 mg/mL microsomal protein to aid in discriminating low clearance compounds
- Quantitation using LC/MS/MS
- Results delivered within a 1-2 week turnaround time
- Data reported as percent of test article remaining after incubation time and in vitro half-life

[bdbiosciences.com](http://bdbiosciences.com)

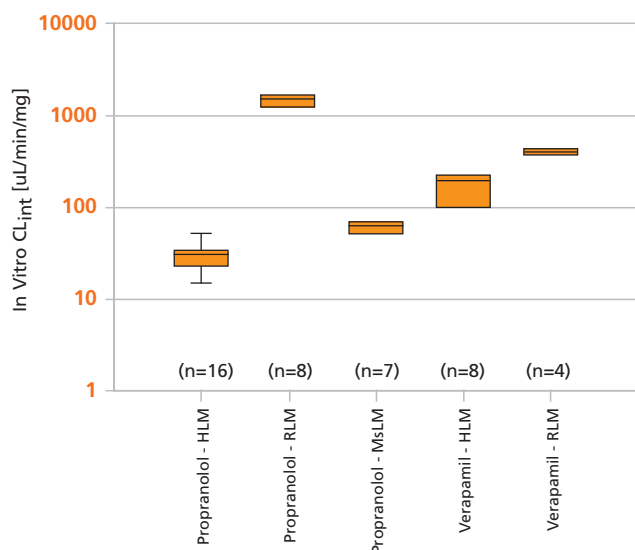
To inquire about BD Gentest<sup>SM</sup> Contract Research Services, contact 888.334.5229 x2246 or 781.935.5115 x2246. Outside the U.S., visit [bdbiosciences.com/offices](http://bdbiosciences.com/offices) to locate your nearest BD Biosciences office.



# METABOLIC STABILITY IN MICROSOMES

## SPECIFICATIONS:

### HISTORICAL ASSAY PERFORMANCE FOR METABOLIC STABILITY IN HUMAN, RAT, AND MOUSE LIVER MICROSOMES



In vitro intrinsic clearance results obtained for positive control compounds in human (HLM), rat (RLM), and mouse (MsLM) liver microsomes. Boxes represent the 25th-75th percentile, the line marks the median, error bars indicate the 90th and 10th percentiles. Data was obtained using multiple lots of microsomes.

### COMPARISON OF IN VITRO INTRINSIC CLEARANCE RESULTS WITH LITERATURE DATA

Substrate	Cl <sub>int</sub> [uL/min/mg]	Literature Cl <sub>int</sub>
Diazepam	20 18	3 <sup>[1]</sup>
Diltiazem	64 45	34 <sup>[3]</sup> , 27 <sup>[2]</sup>
Omeprazole	45 28	34 <sup>[3]</sup> , 97 <sup>[5]</sup> , 12 <sup>[2]</sup>
Dextromethorphan	56 33	22 <sup>[2]</sup>
Phenacetin	25 18	9 <sup>[2]</sup>
Midazolam	≥ 140 ≥ 140	160 <sup>[4]</sup>
Propranolol	33 22	13 <sup>[1]</sup> , 11 <sup>[2]</sup>
Verapamil	≥ 140 ≥ 140	122 <sup>[1]</sup> , 138 <sup>[2]</sup>
Nicardipine	≥ 140 ≥ 140	1719 <sup>[1]</sup>
Imipramine	27 12	19 <sup>[4]</sup>
Diclofenac	105 53	80 <sup>[2]</sup> , 189 <sup>[4]</sup>
Gemfibrozil	47 116	47 <sup>[6]</sup>

Comparison of in vitro intrinsic clearance results obtained at BD using human liver microsomes (1 μM substrate concentration, 0, 10, 20, 30 min. time points) with literature data. Values are means of duplicates repeated on two separate days.

## STUDY DESIGN SUMMARY

<b>TEST SYSTEM:</b>	BD Gentest™ tissue fractions (human and animal liver microsomes, S9, cytosol) or sponsor's custom pooled microsomes.
<b>PROTEIN CONCENTRATION:</b>	0.5 – 1.0 mg/mL.
<b>POSITIVE CONTROLS:</b>	Suitable substrate for each enzyme source (e.g. verapamil for HLM).
<b>TIME POINTS:</b>	For screening: 1 non-zero time point (e.g. 0 + 60 min). For in vitro half-life determination: 4 non-zero time points. (e.g. 0, 5, 10, 20, 30 min).
<b>ANALYTICAL METHOD:</b>	LC/MS/MS.
<b>CONCENTRATIONS:</b>	Single test article concentration, in duplicate.
<b>REPORT:</b>	Percent loss, half-life Excel data report.

## References

- [1] Riley RJ et al. (2005) Drug Metab. Dispos. 33:1304. [4] Obach RS (1999) Drug Metab. Dispos. 27:1350.  
 [2] Soars MG et al. (2003) Br. J. of Clin. Pharmacol 55:175. [5] Naritomi Y et al. (2001) Drug Metab. Dispos. 29:1316.  
 [3] McGinness DF et al. (2000) Drug Metab. Dispos. 28:1327. [6] Andersson TB et al. (2004) Drug Metab. Dispos. 32:715.