



Personalised services in drug discovery

## Metabolic stability

**Metabolic stability is an important property of drug candidates since it affects parameters such as clearance, half-life and oral bioavailability.**

Thus, knowledge of metabolic stability is essential both in drug discovery and development program. By using species-specific liver microsomes


or plasma (e.g., rat, human), stability assays give essential information on a compound's potential pharmacodynamic properties.

### Other early ADMET assays available

 *In vitro* cytotoxicity assay

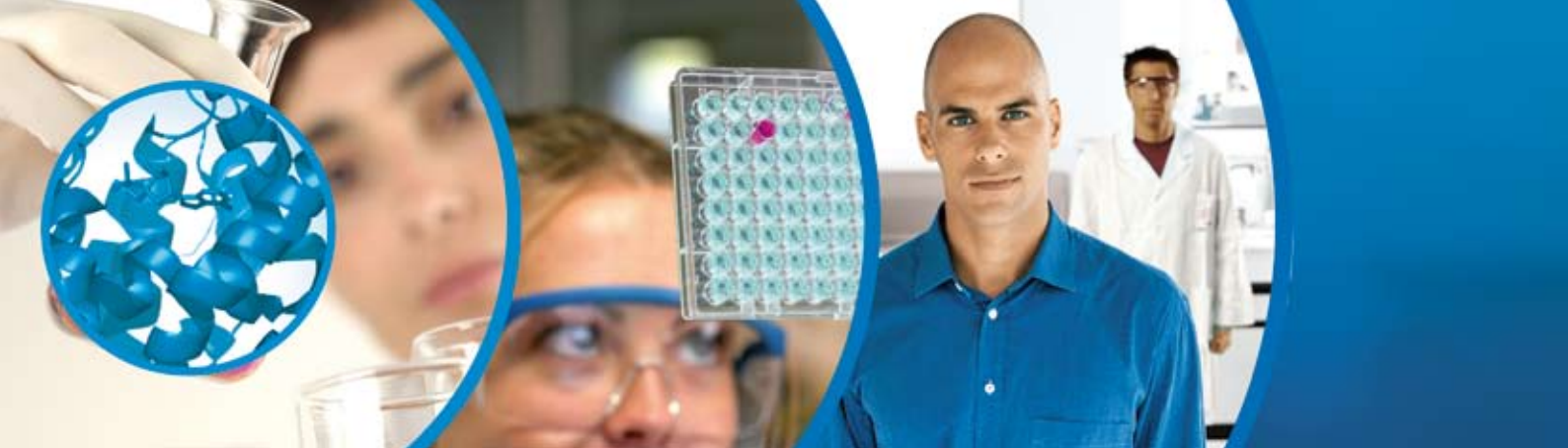
 Kinetic solubility and stability

 Permeability

 Spheroid Model for hepatotoxicity Study

 CYP450 inhibition

 Metabolic assay



# Metabolic stability

## Method

### Microsomal stability

Compounds (1µM final concentration) are incubated with liver microsomes (rat, mouse or human) in potassium phosphate buffer. The microsomal protein concentration in the assay is 1mg/mL and the final percent DMSO is 0.2%. Reaction is started by the addition of NADPH and stopped either immediately or after 15 min for screening assay or at 5, 15, 30 and 60 minutes for a more precise estimate of clearance.

The corresponding loss of parent compound is determined by LC/MS.

Data analysis:

% remaining of compound is calculated compared

to the initial quantity at time zero. Half-life is then calculated based on first-order reaction kinetics.

### Plasma stability

To determine their plasma stability compounds are incubated in plasma of different origins (as requested) and incubated at 37°C. Aliquots of samples are removed at various time points followed by proteins precipitation. % remaining of compound is determined by LC/MS in respect to the amount of compound at time zero.

## Validation of the model

Comparison of our rat microsomal stability assay and published values

Compounds	Average half-life in our model in min	Published* Half-life in min
Indomethacin	> 30	> 30
Promethazine	< 1	0,9
Propranolol	< 1	0,9
Verapamil	5	6

\*Li Di et al., 2006 (317), Int. J. Pharm. p54.

## Classification

Metabolism < 1min: very fast

5 min < Metabolism > 15 min: fast

15 min < Metabolism > 30 min: moderate

Metabolism > 30 min: slow