Pharmacokinetic studies are conducted in compliance with the criteria for reliability of application data (medical device, etc.), agrichemical GLP, and OECD-GLP at the GLP-compliant facility certified by AAALAC International.

In vivo ADME studies using various species of animals are conducted with superior animal science technology. Measurement data are collected online with pharmacokinetic study support system (ADME SUPPORT, Fujitsu), allowing us to provide fast and accurate data.

<table>
<thead>
<tr>
<th>Type of nuclei</th>
<th>Animal species</th>
<th>Administration route</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{14}$C</td>
<td>Rat</td>
<td>Oral</td>
</tr>
<tr>
<td>$^3$H</td>
<td>Mouse</td>
<td>Intravenous</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>Guinea pig</td>
<td>continuous intravenous infusion</td>
</tr>
<tr>
<td>$^{35}$S</td>
<td>Rabbit</td>
<td>Percutaneous</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>Dog</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td></td>
<td>Cynomolgus monkey</td>
<td>Intramuscular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intratracheal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocular instillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intraarticular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intrauterine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intrarectal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intraduodenal</td>
</tr>
</tbody>
</table>

Other administration route and options such as repeated administration are available at your request.
Absorption Study

We have a fast assay system and a reliable frequent blood sampling technique with abundant experience.

Studies using RI-labeled compounds

• Radioactivity concentrations and profiling in blood and plasma (dissolution method, combustion method)
• Calculation of pharmacokinetic parameters using pharmacokinetic analysis software (WinNonlin). Statistical analysis with SAS is also available.
• Identification of absorption sites in the gastrointestinal tract and evaluation of portal absorption.

Studies using non-labeled compounds (PK studies)

• Drug concentration assay with LC/MS/MS, plasma concentration profile, bioavailability, bioequivalence, and drug-drug interaction
• Development of assay system, sample pretreatment method, and analysis conditions of instrument, validation of the assay method. Various evaluations such as stability in blood are available based on the supposition of actual clinical studies.
• A whole set of study process from development of assay system to dosing in animals, sample collection, and assay is available at one facility.
• In assays using RI-labeled compounds, measurement of unchanged form and its metabolites are also available.
• Calculation of pharmacokinetic parameters using pharmacokinetic analysis software (WinNonlin). Statistical analysis with SAS is also available.
Distribution Study

Fractionation of the brain and eyeballs is available upon request. Contact us for your request on other tissues.

**Tissue extraction method**

- Measurement of radioactivity by the dissolution or combustion method.
- Determination of pharmacokinetic parameters for tissue drug concentration using pharmacokinetic software WinNonlin.

**Whole-body autoradiography**

- Measurement of tissue radioactivity concentrations by quantitative whole-body autoradiography (QWBA) method.
- Quantitation/Analysis of radioluminogram using QWBA image analysis software SeeScan (LabLogic Systems limited).
- Tissue radioactivity concentration by QWBA is available among pregnant animals and other animal species such as rabbits and cynomolgus monkeys.
- QWBA radioactivity measurement can be performed with rat brain (striatum, hippocampus, and choroid plexus, etc.).

**Tissue and sample collection**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>1h</th>
<th>4h</th>
<th>8h</th>
<th>12h</th>
<th>24h</th>
<th>48h</th>
<th>72h</th>
<th>168h</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>48h</td>
<td>72h</td>
<td>12h</td>
<td>8h</td>
<td>4h</td>
<td>1h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**QWBA analysis (rat)**

Calibration curve
**Metabolism Study**

**in vivo metabolite profiling**
- We perform profiling of metabolites in plasma, urine, feces, bile, and tissues collected from animals (humans) after administration of a test substance are subjected to the LC-RID/MS measurement to simultaneously acquire radiochromatogram and accurate MS data.
- Evaluated species: Rat, mouse, dog, monkey, rabbit, human, etc.

**in vitro metabolite profiling**
- The species difference and sex difference of a test substance are evaluated using hepatocytes or cell fractionations obtained from experimental animals or humans in *in vitro*. The structure elucidation of metabolites can be conducted at the same time.
- Evaluated species: Rat, mouse, dog, monkey, human, etc.
- Origin:
  - Microsomes (Liver, kidney, small intestine, etc.)
  - S9 (Liver, kidney, etc.)
  - Hepatocytes

**Metabolite structure estimation**
- Structure elucidation of metabolites by accurate mass analysis
- Mass spectrometry is available with labeled test substances.

LC/MS™: LTQ Orbitrap XL (Thermo Fisher Scientific)
We have abundant experience with bile excretion and enterohepatic circulation in dogs and monkeys.

**Excretion rates into urine, feces, expiration, and bile and enterohepatic circulation**

- Bile samples can be collected over time not only in small animals but also in large animals.
- Bile samples can be collected over time by free-moving method (Ballman’s cage for rats).

**Dosing**

- 72h
- 168h
- 48h
- 24h
- 8h

**Urine, feces, expiration, bile collection**

**Metabolic cage for rats**

**Metabolic cage for dogs**

**Metabolic cage for monkeys**