

# Pharmacokinetics

Understanding the pharmacokinetics of a test article in species typically employed in preclinical testing is an essential component of drug discovery and development programs. At Charles River, we provide a full pharmacokinetic evaluation service utilizing a wide spectrum of dose regimens and administration routes in both rodent and nonrodent species. We are able to support rapid bioavailability screening during drug candidate selection, as well as define the pharmacokinetic profile of compounds in the development phase.

Our study directors have access to colonies of non-naïve animals and excellent surgical capabilities enabling us to offer multiple routes for dosing and sample collection.

## Discovery Screening

Rapid *in vivo* pharmacokinetic screening studies can assist in lead candidate selection from libraries of compounds. Compounds which display unfavorable pharmacokinetic profiles can be quickly excluded, allowing optimization of subsequent analogs.

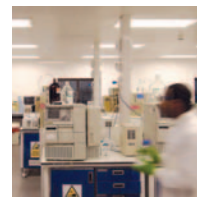
Charles River has a battery of standard study designs which vary from abbreviated sample collection regimens used to assess relative bioavailability to full kinetic sampling of blood and urine. Cassette dosing or plasma pooling coupled with LC-MS/MS analysis are also possible when working with compounds in an analog series. Although formal GLP compliance is not required, these studies are conducted in GLP-compliant facilities, giving clients reassurance of the quality of work performed.

To accelerate study initiation, we maintain a supply of rodents and have colonies of nonrodent species. The colony animals can help you avoid the high cost of naïve animals and quarantine delays.

Preliminary toxicokinetic profiles with limited histopathology support can also be obtained using our lead optimization toxicology program, which is designed to assess potential toxicity as early as possible. This expanded drug discovery service helps bring forward candidates that are more likely to succeed in preclinical testing and, ultimately, in the clinic.

## Study Types

- Discovery screening
  - Cassette dosing
  - Sample pooling
- Bioavailability
- Bioequivalence
- Dose ranging
- Dose proportionality
- Excretion kinetics
- Pharmacokinetics/toxicokinetics
  - Compartmental
  - Non-compartmental



## Development

Experienced scientists within Charles River design and conduct pharmacokinetic studies to examine multiple parameters, such as dose proportionality, bioavailability, and food effects, in both single and multiple dose studies. Steady state, multiple dose, or continuous infusion test article administration can be calculated and verified *in vivo*. Toxicokinetic assessments of systemic exposure can be conducted in parallel or concurrent with ongoing toxicology studies. All study types are conducted in full compliance with GLP requirements.



Pharmacokinetic studies can be conducted using either radiolabeled or nonradiolabeled test articles with a range of analytical support available, including radioassay, LC-MS/MS, HPLC, CE, or immunochemistry. Radiolabeled test articles are most commonly used to investigate excretion kinetics.



Innovative and customized surgical models are available for dosing and pharmacokinetic sampling in order to gain more knowledge on the disposition of the compound. Bile duct cannulation models provide insight on biliary excretion and enterohepatic recirculation, while vascular and portal vein cannulation models are useful to investigate first-pass metabolism. Intestinal access port models permit targeted administration to the gastrointestinal tract.

## Data Evaluation

Qualified pharmacokineticists are on hand to assist in study design, pharmacokinetic modeling, statistical analysis, and data interpretation. We perform pharmacokinetic (PK), toxicokinetic (TK), or pharmacodynamic (PD) analysis on bioanalytical data generated at Charles River or on data sets submitted by clients from preclinical and clinical studies.

To define a pharmacokinetic profile of compounds under development, we offer compartmental and non-compartmental methods to examine multiple parameters using several validated statistical software programs. Data and descriptive statistics will be displayed in tables and figures as appropriate.

## Standard Pharmacokinetic Parameters

- Maximum concentration ( $C_{max}$ )
- Time of maximum concentration ( $T_{max}$ )
- Area under concentration time curve ( $AUC_{0-\infty}$  and  $AUC_{last}$ )
- Volume of distribution ( $V_z$ )
- Clearance (CL)
- Terminal elimination half-life ( $t_{1/2}$ )
- Bioavailability
- Other parameters available upon request