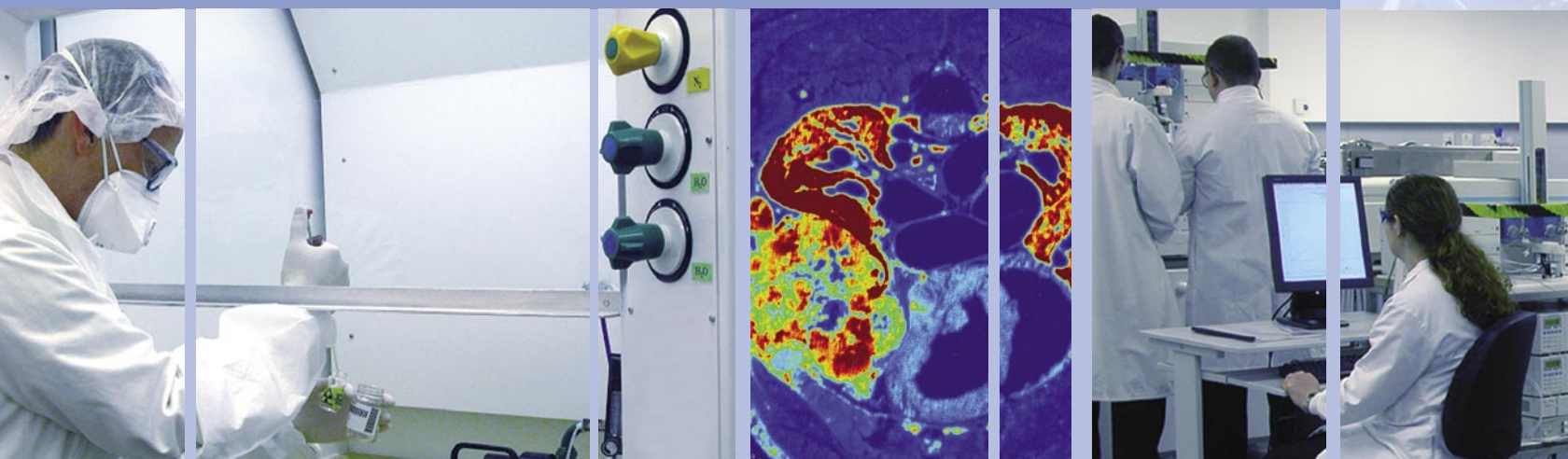


Drug Metabolism and Pharmacokinetics



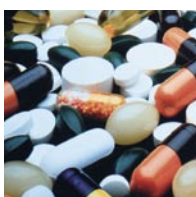

CHARLES RIVER
LABORATORIES



Drug Metabolism and Pharmacokinetics



Charles River Laboratories has long been recognized as a premier global provider of drug metabolism services to the pharmaceutical industry.



Our Drug Metabolism and Pharmacokinetics (DMPK) teams work closely together to provide a complete and complementary service in a GLP environment. We have scientists dedicated to both discovery and development, allowing lead candidate selection to flow seamlessly into the development phase. Development studies are designed to satisfy the requirements of international regulatory authorities and to provide safety data to assess the validity of laboratory species as appropriate toxicological models for man.

Our *In Vitro* Metabolism group supports both discovery and development programs by performing studies to investigate metabolic stability, P450 induction and inhibition, reaction phenotyping, extrahepatic and non-P450 metabolism, and drug absorption.

The *In Vivo* Metabolism group conducts studies to investigate the disposition of radiolabeled and non-radiolabeled test articles in laboratory species and man as part of the development of new pharmaceuticals.

Fully networked and validated data management systems are used in data capture, storage, and evaluation.

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In Vitro Metabolism

The *In Vitro* Metabolism group provides qualitative and quantitative analyses of radiolabeled and non-radiolabeled compounds in a range of *in vitro* test systems. Studies are designed to complement the metabolism, toxicokinetic, and bioanalytical investigations undertaken in pharmaceutical product development.

By providing critical information early in the drug discovery and development process, our automated ADMET screening assays help clients identify and focus efforts on compounds that have the greatest likelihood of success.

Other laboratory assays that complement our *in vitro* metabolism services include cell proliferation, cytotoxicity, hERG, and protein binding.

Absorption, Distribution, Metabolism, and Excretion

Charles River conducts a complete range of *in vivo* metabolism studies in support of lead candidate selection or regulatory submission. The studies are designed to investigate the absorption, distribution, metabolism, and excretion (ADME) of novel compounds in laboratory animal species and man.

Individual protocols are developed in conjunction with our clients to satisfy international regulatory requirements. Where appropriate, work is conducted to meet the requirements of GLP and reports are subjected to Quality Assurance audit prior to issue.

In Vitro Assays

- Enzyme inhibition and induction
- Drug-drug interaction
- Reaction phenotyping
- P450/UGT identification
- Metabolic stability
- Cell permeability
- Aqueous solubility
- Melanin binding
- Skin absorption models

Study Types

- Protein binding
- Plasma kinetics
- Excretion balance
- Biliary excretion
- Enterohepatic recycling
- Tissue distribution
- Placental transfer
- Milk secretion
- Biotransformation



Capabilities

- Discovery screening
- Animal colonies
- Dose ranging
- Bioanalysis
- Data evaluation
- Bioavailability
- Bioequivalence
- Dose proportionality

ADME Dose Routes

- Oral
- Intravenous
- Subcutaneous
- Intraperitoneal
- Continuous infusion
- Transdermal
- Ocular and intravitreal
- Intratracheal and inhalation
- Via access ports
 - Portal vein
 - Gastrointestinal tract

Applications

- Localization of tissue exposure
- CNS penetration and distribution
- Placental transfer
- Bone marrow exposure for *in vivo* mutagenicity
- Tumor targeting
- Dosimetry studies

Pharmacokinetics

Charles River excels in conducting discovery and development pharmacokinetics studies. This service includes discrete or cassette dosing studies for screening multiple compounds and conventional GLP studies designed for product registration purposes.

Our scientists have direct access to Charles River's research models, unique surgical models, and sizeable colonies of non-naïve animals for immediate use in any study.

Bioanalysis of the collected samples is available and qualified pharmacokineticists are on hand to assist in study design, pharmacokinetic modeling, statistical analysis, and data interpretation.

Mass Balance

Development scientists design and conduct mass balance studies in a variety of species. Studies routinely use radiolabeled molecules to fully describe the rate and routes of elimination of the administered radioactivity. The samples generated are also used to provide information on the biotransformation of the parent drug.

We have expertise in a wide range of preclinical laboratory species and dose routes, allowing us to fully meet the needs of most development programs.

Quantitative Whole Body Autoradiography

Quantitative Whole Body Autoradiography (QWBA), now commonplace in regulatory submissions, is a powerful tool used to evaluate the tissue distribution of drug candidates. In addition to quantitative tissue concentration data, the relative distribution of radioactivity within organ substructures can be assessed and quantified. Charles River was one of the first Contract Research Organizations (CROs) to commercially embrace this technology and offer QWBA distribution studies to GLP requirements.

Besides supporting development studies, this technique is utilized in drug discovery to assess target tissue penetration of potential drug candidates. QWBA is suitable for use with all rodent species, as well as some nonrodent species, and the technique can be used with a variety of radioisotopes.

Surgical Services

Charles River offers a diverse range of surgical models and services developed in accordance with the most recent advances in surgical procedures and animal welfare. Our research surgeons have extensive experience in a variety of rodent and large animal species.

A number of chronic surgical models are available within our non-naïve animal colonies that allow specialized dose routes to be used and multiple sample collections to be undertaken. Availability of colony animals facilitates rapid initiation for most study types. The same surgeons who developed these sophisticated surgical procedures are available to assist in the creation of the most relevant animal model for an enhanced understanding of your compound.

Clinical Metabolism

An early understanding of the metabolism of a drug candidate in human subjects is increasingly being considered by the pharmaceutical industry as a critical step in the development process. We recommend that these studies are conducted during early Phase II clinical development in order to have confidence in the safety profile of a drug candidate before testing the drug in a wider patient population.

Charles River's position as a CRO with both preclinical and clinical facilities has allowed us to build considerable expertise in this area of research over many years. Our Phase I clinical facility has been designed to accommodate the specific metabolism study requirements related to sample custody and accountability. This has allowed us to maintain a high-quality service and we are recognized within the industry as a specialist in this field.

In addition to conducting a full-service study in our own facilities, we also accept labeled samples for analysis from other clinical trials.

Surgical Models

- Vascular access ports
- Intravenous infusion
- Cannulation
 - Bile duct
 - Intrathecal
 - Intrahepatic
 - Intracerebral ventricular
 - Intracystic
 - Intestinal
 - Hepatic portal vein
- Cerebrospinal fluid sampling
- Lymph collection
- Urinary catheter

Services

- Regulatory support
- Repurification of Active Pharmaceutical Ingredient (API)
- Investigational Medicinal Product (IMP) manufacture
- Qualified Person (QP) release
- Central Laboratories
- Pharmacovigilance
- Biotransformation
- Data management
- Medical report writing

Technical Capabilities

- Radiometric profiling
- HPLC
- LC-MS
- LC-MS/MS
- GC-MS
- Ion Trap MS
- CE for oligonucleotides
- TOF and MALDI-TOF
- Organic chemistry metabolite synthesis

Biotransformation

Isolation, analysis, identification, and stability of metabolites in biological matrices can be critical to the understanding and interpretation of ADME studies. Characterization of metabolites in biological samples can be undertaken either as a natural conclusion to other metabolism or kinetic studies performed at Charles River, or as a stand alone study, using samples or sample extracts provided by a client.

Additionally, a synthetic chemistry service is available to undertake synthesis of metabolites, reference standards, and internal standards to assist with method development and metabolite identification.

Humane Care

Each of our facilities is committed to scientific excellence, high-quality service, and ethical business practices. At Charles River, ethical conduct extends to the humane care of research animals through uncompromising animal welfare standards as directed by our Humane Care Initiative.

The use of laboratory animals furthers our knowledge of living systems and contributes to the discovery of life-saving drugs and procedures. Therefore, as animal caregivers and researchers, we are responsible to our clients and the public for the health and well-being of the animals in our care.

We also maintain the highest ethical standards in all aspects of our clinical work. The safety, well-being, and dignity of the volunteers and subjects who participate in our clinical trials are of paramount importance.

We believe that good medicine is the result of good science - the stakes are simply too high to accept less.

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