charles river

SAFETY ASSESSMENT

Drug Metabolism

It is important to understand the key role that drug metabolism and drug-drug interactions play in the efficacy and safety elements of the drug discovery and development process. At Charles River, we help our clients identify the metabolic pathways, potential interactions and routes of elimination of their compound at an early stage.

We have scientists dedicated to both discovery and development, allowing lead candidate selection to flow seamlessly into the development phase. Our discovery and research specialists offer customized screening programs to ensure early and late lead candidate optimization. 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 humans. Our drug metabolism facilities are networked and utilize validated data management systems for data capture, storage and evaluation.

We offer a comprehensive range of drug metabolism services. With our scientific depth, regulatory knowledge and technical expertise, we help our clients accelerate the development of safe and effective therapies.

Areas of expertise:

- Discovery and research services
- *In vitro* metabolism
- Absorption, distribution, metabolism and excretion (ADME)
- Pharmacokinetics
- Mass balance
- Labeled and label-free tissue/whole-body imaging
- Surgical services
- Clinical metabolism support
- Biotransformation
- Laboratory sciences

EVERY STEP OF THE WAY

Discovery and Research Services

Early attrition of unsuitable drug candidates is key to the successful development of a new therapeutic. *In vitro* ADME-Tox (ADMET) and *in vivo* pharmacokinetic (PK)/ADME screening provide valuable information to help our clients prioritize and accelerate their drug discovery process from compound ranking to lead candidate selection. These services are just part of a full range of discovery and research services offered at Charles River which also includes pharmacology models of disease and formulation development, as well as phenotyping and biomarker services.

In Vitro Metabolism

By providing critical information early in the drug development process, our ADMET screening assays help identify and focus efforts on compounds that have the greatest likelihood of success. Once a lead candidate is selected, both qualitative and quantitative analyses of radiolabeled and nonradiolabeled compounds are provided in a range of *in vitro* test systems. Studies are designed to complement the metabolism, toxicokinetic (TK) and bioanalytical investigations undertaken in pharmaceutical product development. Other laboratory assays that balance our *in vitro* metabolism services include cell proliferation, cytotoxicity, hERG blockade and protein binding.

Absorption, Distribution, Metabolism and Excretion (ADME)

Charles River offers a complete range of *in vivo* metabolism studies in support of lead candidate selection, preclinical testing and clinical development programs. The studies are designed to investigate the ADME properties of novel compounds in laboratory animal species and man. Our experienced scientists routinely conduct mass balance and tissue distribution studies to determine tissue half-life, clearance rates and potential sites of toxicity after systemic exposure. Individual protocols are developed collaboratively with our clients to satisfy the appropriate international regulatory requirements.

Pharmacokinetics

We excel in conducting discovery and developmental PK studies. This service includes discrete or cassette dosing studies for screening multiple compounds and conventional GLP PK and TK studies designed for product registration purposes. Our scientists have direct access to our world-renowned research models, unique surgical models and colonies of nonrodent species. Bioanalysis of the collected samples is available, and qualified pharmacokineticists are on hand to assist in study design, PK modeling, statistical analysis and data interpretation.

Mass Balance

Our scientists design and conduct mass balance studies in a variety of species. Studies routinely use radiolabeled compounds 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 product development programs.

Labeled and Label-Free Tissue/Whole-Body Imaging

Quantitative whole-body autoradiography (QWBA) is a powerful tool used to evaluate the tissue distribution of drug candidates. As well as 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 (e.g., minipigs and nonhuman primates of body weight < 10 kg), and the technique can be used with a variety of radioisotopes.

Offered in collaboration with ImaBiotech, MALDI-MSI (matrix-assisted laser desorption/ionization mass spectrometry imaging) provides a label-free imaging alternative for the detection and localization of drugs and drug metabolites. Ideally suited to assessing the intra-organ distribution of drugs and their metabolites, MALDI-MSI can be successfully adapted to provide whole-body images in small rodent species. Furthermore, using proprietary software, quantitative data can be produced.

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 the development of sophisticated surgical procedures in a variety of rodent and large animal species, and are available to assist in the creation of the most relevant animal model for an enhanced understanding of novel compounds.

Clinical Metabolism Support

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 be conducted during early Phase II clinical development to ensure confidence in the safety profile of a drug candidate before testing the drug in a wider patient population. We can support the specific metabolism study requirements related to sample custody analysis and accountability.

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 part of other metabolism or kinetic studies performed at our facilities, or as a stand-alone study using samples or sample extracts provided by our clients. Our synthetic chemists further support method development and metabolite identification through the synthesis of metabolites, and application of reference standards and internal standards.

Laboratory Sciences

Each well-designed *in vitro* and *in vivo* study must have the appropriate analytical tools to obtain meaningful data; thus, advanced laboratory technology is key to a program's success. Charles River continuously invests in highly-trained scientists and state-of-the-art facilities and instrumentation to increase our capabilities and capacity to produce rapid and reliable data. Support services include formulation development, analytical chemistry, bioanalysis, immunology and radioanalysis.